ANNALS OF
INTERNAL MEDICINE

VOLUME 54 JANUARY, 1961 NUMBER 1

FUNCTIONAL SUBAORTIC STENOSIS * †

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ADVANCES in cardiovascular surgery have naturally stimulated a re-evaluation of valvular lesions which may be amenable to surgical correction. Although subaortic stenosis of the left ventricular outflow tract was first described by Chevers [1] in 1832, its functional significance has been largely ignored. The inability to substantiate at surgery many preoperative diagnoses of aortic valvular obstruction based on the demonstration of a left ventricular-aortic gradient has stimulated interest in other causes of obstruction to flow. A precise differential diagnosis of supravalvular, valvular, and subvalvular outflow tract obstruction is critical in the selection of the appropriate surgical procedure. Until quite recently, stenotic lesions of the paravalvular areas were considered to be essentially benign and extremely rare.[2-7] There were less than 50 cases reported in the cardiac literature prior to 1950, and most of the authors considered the lesion to be compatible with a normal life span. More recent reports, however, have indicated an increase in frequency of recognition of these lesions. Brock [8, 9] reported 12 cases diagnosed during life and suggested that the subaortic fibrous lesion may be as common as the valvular. Rudolph [10] was able to make this diagnosis in five patients over a two-year period. Hancock,[11] reporting a series of patients, stated that severe aortic stenosis is

* Received for publication May 13, 1960.
Presented at the Forty-first Annual Session of The American College of Physicians, San Francisco, California, April 4–8, 1960.
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† This work was supported by grants from the U. S. Public Health Service (NIH H-2637), the Kriendler Memorial Foundation, and the Massachusetts Heart Association.
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subvalvular in 15% of all cases and in nearly 50% of those under 25 years of age.

The prognosis is generally poor. A review of the literature bears testimony to the frequently fatal complications that are associated with the lesion. Bacterial endocarditis may affect the uninvolved aortic valve as well as the subaortic lesion.[4, 12-17] The use of antibiotics, however, in the treatment of subacute bacterial endocarditis has resulted in greater longevity for these patients. Most of them now go on to develop persistent and severe left ventricular outflow tract obstruction, leading to congestive heart failure, angina pectoris, syncope, or sudden death. We have studied six patients with this defect—four males and two females, 13 to 42 years of age.[18] Aortic pressure gradients were established by cardiac catheterization. Five

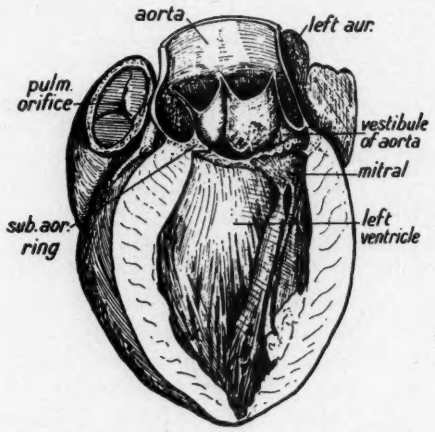

FIG. 1.* Diaphragmatic representation of a subaortic "ring-diaphragm" (Keith). Note the involvement of the aortic leaflet of the mitral valve and septal hypertrophy in the region immediately beneath the ring.

patients were observed at operation and four subsequently examined postmortem. In the sixth patient, a subaortic chamber was demonstrated by retrograde aortic catheterization.

The pathogenesis of functional aortic stenosis, classically defined as a ring of fibrous tissue 5 to 22 mm. below the aortic cusps which encircles the aortic conus and includes the anterior cusp of the mitral valve, was described at the turn of the century by Sir Arthur Keith.[19-21] Figure 1, reproduced from the original paper, shows the fibrous ring, the "third chamber" (labeled "vestibule"), and the position of the septum vis-à-vis the outflow tract. He felt that the condition represented embryonic maturation arrest with persistence of the primitive bulbus cordis. In the three-chambered vertebrate heart, this tissue functions as a separate muscular chamber between the

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common ventricle and the aorta. As embryonic growth progresses, the major portion of this tissue is incorporated into the infundibulum of the right ventricle. There is total atrophy of that portion represented in the "left" heart. Although arrest of growth of the bulbus in the right heart will lead to infundibular pulmonic stenosis, arrest of atrophy in the left may lead to subaortic stenosis. A remnant of tissue may persist as the more familiar subaortic fibrous band, or arrest may occur while it is still a contractile muscular structure, so that it remains an intrinsic functional portion of the interventricular septum. A recent report by Brent et al.[22] describes "functional" subaortic muscular obstruction occurring in two families over three generations, and suggests that the lesion is inherited as a Mendelian dominant trait.

TABLE 1

Classification of Subaortic Stenosis

I. Congenital
   A. Band type (fibrous)
   B. Diaphragmatic type
      Both with or without 1° congenital septal myocardial hypertrophy (remnant of bulbus cordis)

II. Familial (? Mendelian dominant inheritance)
   A. Septal myocardial hypertrophy

III. Acquired or Developmental
   A. Endocardial sclerosis secondary to trauma or mural inflammation
   B. Muscular
      1. With subaortic stenosis (fibrous)
      2. With aortic stenosis, rheumatic or congenital
      3. With hypertension
      4. Miscellaneous
         a. Mitral insufficiency
         b. Bicuspid aortic valve
         c. Coarctation
         d. Bacterial endocarditis
         e. Idiopathic myocardial hypertrophy
         f. Luetic aortitis

The most commonly associated congenital anatomic abnormalities appear to be "bicuspid aortic valve" [8, 9, 23–26] and coarctation of the aorta.[26, 27] A case has also been reported of an associated congenital aneurysm of the interventricular septum.[28] Recently, at The New York Hospital, subaortic stenosis was found together with an aneurysm of the sinus of Valsalva [29]; this patient succumbed to intractible congestive heart failure following bacterial endocarditis which destroyed a previously normal aortic valve. Pulmonic stenosis, although embryologically predictable as a concurrent lesion, has only rarely been reported. In this series, however, mild pulmonic stenosis was found in two of six patients, suggesting that lack of recognition in earlier reports may have been due to lack of catheterization data. Mitral insufficiency due to intrinsic involvement or interference with leaflet apposition by asymmetric hypertrophy has also been reported from laboratories where the lesion was sought for specifically.

Classification

The classification of subaortic stenosis is shown in Table 1.

A physiologic description of the left ventricle in systole accentuates the importance of proper muscular apposition of the functional components of the outflow tract for complete, unobstructed, systolic emptying. Brock's report of acquired subvalvular stenosis was the first appreciation that myocardial hypertrophy alone, from whatever cause, could be responsible for significant outflow tract obstruction. Indeed, the late appearance of slowly progressive symptoms of aortic obstructive disease in patients with known congenital subaortic stenosis suggests that those cases unassociated with primary congenital myocardial septal hypertrophy may develop secondary septal obstruction as the myocardium slowly hypertrophies in response to moderate obstruction to flow. In post-mortem examinations with total relaxation of the dilated heart, the thickened septal element pouching into the outflow tract of the left ventricle can easily be missed by the conventional methods of pathologic examination, and accounts, perhaps, for the comparative rarity of the pathologic diagnosis. The unopened ventricular chamber must be observed by looking downward through the aortic valve. Indeed, it may require simulation of contraction to visualize the mechanism by which the hypertrophied septum moves into the outflow tract to form a major obstruction to flow. This type of systolic (contraction) stenosis may occur secondarily to any cause of concentric myocardial hypertrophy involving the septum. Systolic muscular stenosis may even be the important element in the classical diaphragmatic-band subaortic stenosis. In actual fact, the size of the orifice as measured at autopsy does not offer a major hydraulic obstruction. Only when the ring of tissue is thrust into the outflow tract by a hypertrophied septal wall is this true.

Diagnosis

Unfortunately, there are no absolute criteria for diagnosis (Table 2). The lesion is suggested by a combination of several clinical and laboratory findings, each confirmatory, but none individually diagnostic. Atypical signs in a patient presumed to have aortic stenosis are perhaps of greatest significance. The history is of little help in the differential diagnosis, serving only to establish a congenital etiology for the lesion.

The physical examination, however, may yield several clues. Our patients all had a loud, harsh, "diamond-shaped" systolic murmur. Although the murmur is frequently heard in the first and second intercostal spaces to the right of the sternum, it may often be loudest along the left sternal border or even at the apex. Indeed, the murmur may be virtually absent over the aortic area itself. A thrill frequently accompanies the murmur and may be transmitted into the neck, but this occurs less consistently with the subvalvular than with the valvular lesion. An aortic ejection click is heard

in many cases of noncalcific aortic valvular stenosis, but it is not usually present in subvalvular stenosis.

Although the diagnostic significance of an audible second sound which may be heard in valvular stenosis is frequently disputed, the sound is supportive evidence for a subvalvular lesion. Conversely, the absence of an aortic second sound is of little significance, since associated valvular involvement, the so-called "double stenosis," may be present.

A diastolic murmur, once thought to be important evidence *against* the diagnosis of a subaortic lesion, has not proved to be a reliable sign. Left sternal border or basilar diastolic murmurs were noted in three of our six patients and have been described by other authors. This murmur may

TABLE 2

Diagnosis of Subaortic Stenosis

1. Atypical findings of aortic stenosis
2. History
3. Physical examination
   a. Systolic murmur, thrill, and ejection click
   b. A-2
   c. Diastolic murmur
   d. Blood pressure
4. Electrocardiogram
5. X-ray
   a. Absence of calcification of aortic valve
   b. Absence of dilatation of first part of aorta
   c. Selective angiocardiography
6. Arterial pulse tracing
   a. Anacrotism
   b. Percussion wave
7. Retrograde or left heart catheterization
8. Open inspection and palpation

represent actual back-flow of blood from a high to a low pressure area, due to delayed or "consecutive" systole of what has now become a subdivision of the left ventricular chamber.

Sphygmomanometry is of little help in the evaluation of either aortic or subaortic stenosis. The electrocardiogram is also unimportant in the differential diagnosis. X-ray examination, particularly angiocardiography, has made the greatest contribution toward identifying this abnormality. Valvular calcification is noted in 87% to 97% of cases of aortic valvular stenosis, whether of congenital or rheumatic etiology.[30] Its presence varies directly with advancing age, being found in a significant number of patients over the age of 30, in the majority of patients over 40, and in better than 95% of patients over 50 years of age. Fluoroscopy is often of greater value than are conventional chest films in locating these calcific areas. Dilatation of the first portion of the aorta is the most consistent roentgen abnormality in aortic stenosis and is found in over 80% of these patients.[17, 31-33] Conversely, aortic dilatation is *absent* in over 90% of patients with

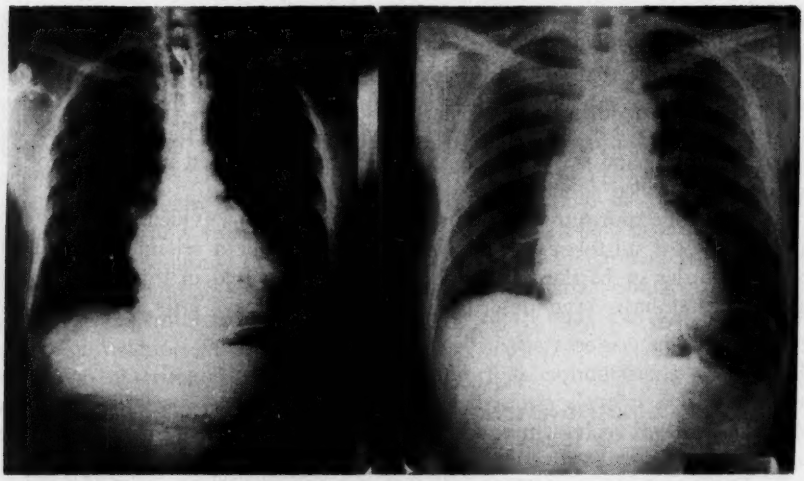

FIG. 2.* Cardiac x-rays in subaortic and aortic stenosis. The x-ray on the left is that of patient J. F. Note the nonspecific enlargement, left ventricular prominence, and absence of post-stenotic aortic dilatation. The x-ray on the right is from a patient with proved valvular aortic stenosis. In contrast, note the striking post-stenotic dilatation of the aorta.

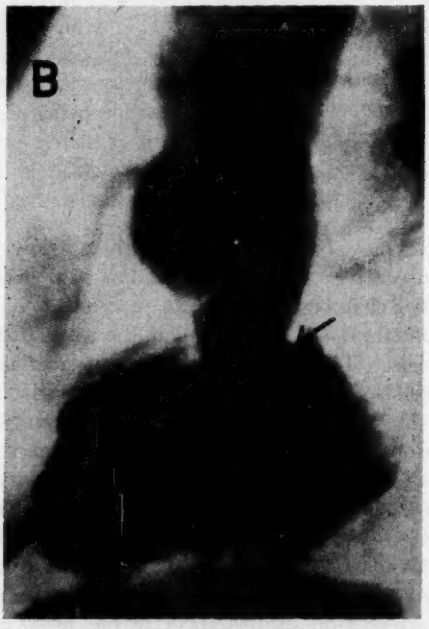

FIG. 3.* Demonstration by angiocardiography of the existence of a true subaortic chamber (taken from Bjork).

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proved subaortic stenosis.[34-36] In Figure 2 the x-ray on the left is that of one of the patients in the subaortic group. Note the nonspecific enlargement, left ventricular prominence, and absence of post-stenotic aortic dilatation. In contrast, the x-ray of the patient on the right, who had proved aortic *valvular* stenosis, shows striking post-stenotic dilatation of the first portion of the aorta. Figure 3, taken from Bjork,[26] showing a study using dye injection introduced by left ventricular puncture, clearly demonstrates not only the valve and the subaortic obstruction (marked by an arrow),

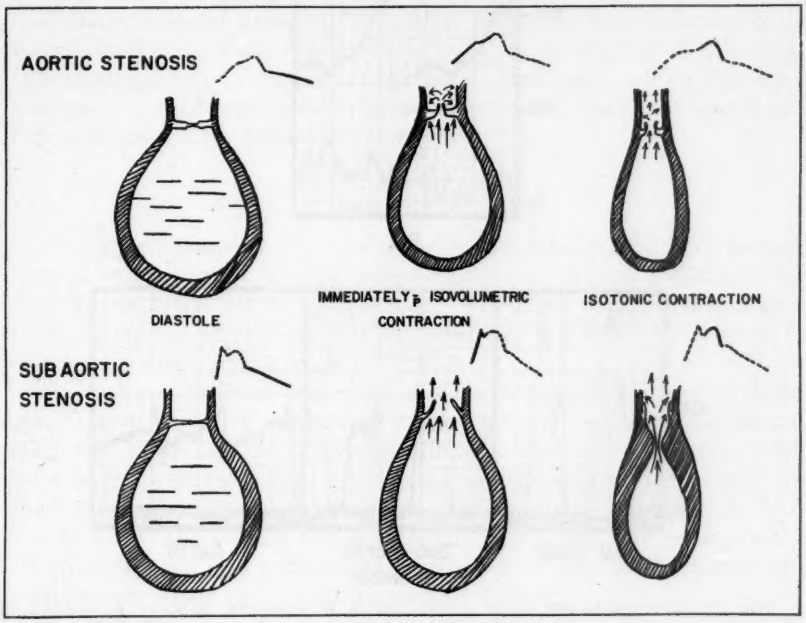

FIG. 4.* Mechanics of arterial pressure pulse formation in aortic stenosis and subaortic stenosis. In the former, a fixed orifice obstruction is presented to the contracting ventricle with resultant early eddy formation. In subaortic stenosis the obstruction develops progressively with the onset of isotonic contraction so that there is escape of a percussion wave at the inception of systole.

but an actual physiologic "third chamber" interposed between the ventricle and the aorta itself. More recent methods utilizing retrograde selective cardiographic technics eliminate the hazard of left atrial or ventricular puncture.

The arterial pulse tracing is of value only when it lends support to the other diagnostic criteria enumerated. Pure band or diaphragmatic obstruction may reproduce the tracing of valvular aortic stenosis. Hemodynamically, both types represent a fixed obstruction. Muscular subaortic obstruc-

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tion, whether of the primary "congenital" type or secondary to hypertrophy, is a dynamic phenomenon. Figure 4 is a hypothetic representation of the mechanism of arterial pressure pulse formation in aortic and muscular *sub*-aortic stenosis. The solid lines in the pulse tracing correspond in time to the functional position of the ventricle at their inscription. In aortic stenosis a fixed orifice obstruction is presented to the contracting ventricle. This results in the classical "tardus" pulse tracing. In contrast, muscular sub-

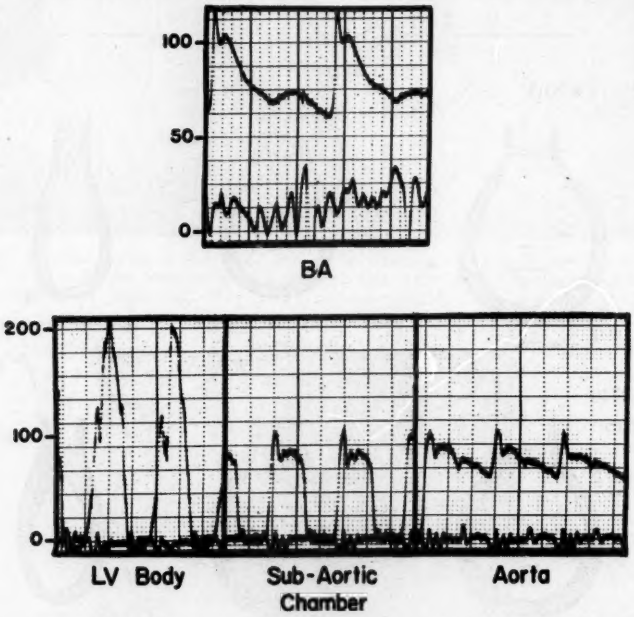

FIG. 5.* Retrograde left heart catheterization in subaortic stenosis. A withdrawal pressure tracing illustrates the drop in diastolic pressure at the valve orifice. There is no systolic gradient across the valve, but as the subvalvular stenosis is traversed and left ventricular pressure recorded, a 110 mm. Hg peak systolic gradient is measured. The upper figure illustrates the rapid escape percussion wave recorded from the brachial artery. Note a similar wave in the subaortic chamber and in the aorta. (Pressure tracing courtesy Dr. A. Rudolph.)

aortic stenosis presents a different physiologic obstruction to flow. With each opening of a normal aortic valve at the end of isometric contraction, a normal percussion wave escapes. With continued *isotonic* contraction, the hypertrophied septal portion of the outflow tract moves into the outflow tract, obstructing flow and setting up eddy currents which delay total ejection. This secondary "tidal" peak often coincides in time with the delay seen in pure valvular stenosis.

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Retrograde left heart catheterization via a systemic artery with continuous pressure recording will reveal a drop in *diastolic* pressure at the valve orifice. Usually, there is no systolic gradient across the valve. As the subvalvular stenosis is traversed, a rise to full ventricular systolic pressure is measured and the intraventricular pressure gradient visualized (Figure 5). The upper part of the figure illustrates the rapid escape-percussion wave recorded from the brachial artery. Note concordance of this wave in the subaortic chamber as well as in the aorta. The percussion peak is *not* seen in the left ventricular tracing itself.

Finally, surgical exposure with open inspection and palpation of the valvular and subvalvular areas may be necessary to establish the diagnosis. It is important to note that even with this examination, significant subaortic muscular "systolic" obstruction may be missed unless the septal area is carefully examined in the beating heart *during* systole.

Conclusions

Congenital subaortic stenosis or developmental so-called "mid-systolic" stenosis poses a major hemodynamic problem for which a satisfactory surgical approach has yet to be developed. A review of recent case reports substantiates our impression that patients with this defect show little tolerance for major surgical trauma.[18, 22, 37]

Recognition of these obstructive lesions will probably increase in frequency as more clinicians become aware of their functional significance. Diagnosis is possible only through clinical suspicion. The most helpful features are evidence of left ventricular strain, atypical location of an aortic ejection murmur, absence of aortic valve calcification or post-stenotic dilatation by x-ray, and absence of the anacrotic pulse wave. Diagnosis depends on demonstration of a subvalvular chamber by retrograde intraventricular pressure recordings or by contrast ventriculography.

Summario in Interlingua

Stenosis systolic functional del via de effluxo del ventriculo sinistre es un lesion non incommun le qual pote simular stenosis aortic valvular. Le etiologia pote esser congenite o acquirite (usualmente in association con un morbo que duce ad hypertrophia sinistro-ventricular). Le lesion es frequentemente associate con pulmonostenosis infundibular, e occasionalmente illo interfere in le function del orificio del valvula mitral.

Stenosis subvalvular es differentiate ab stenosis valvular per le constatation de un loco atypic del murmure de ejection aortic, del absentia de calcification valvular o de dilatation post-stenotic in le roentgenogramma, e del absentia de anacrotismo in le pulso arterial. Le diagnose definitive depende del demonstration de un camera subvalvular per registrationes retrograde de pression intraventricular o per ventriculographia a contrasto.

Therapia chirurgic al tempore presente es non solmente inadequate, illo pote devenir disastrose.

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ERRATA

Vol. 51, No. 4, October, 1959, "The Management of Abnormal Bleeding following Extracorporeal Circulation," by H. A. Perkins, J. J. Osborn, and F. Gerbode. Last line, page 660, should read 300 units instead of 3,000; first line, page 661, should read 2,500 units instead of 25,000.

Vol. 53, No. 6, December, 1960, "Pulmonary Emphysema: Etiologic Factors and Clinical Forms," by Dickinson W. Richards. Line 3 of Table 2 should read (for patient W. D.) 37 instead of 17 Max. Br. Cap., L./min.

RHEUMATOID SPONDYLITIS: A FOLLOW-UP STUDY *

By Aaron M. Lefkovits, M.D., F.A.C.P., and J. R. Thomas, M.D.,
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In July, 1958, we described [1] the clinical manifestations of rheumatoid spondylitis in 267 patients who were observed in our institution from 1947 to 1958. The management of their disease was discussed and the results were tabulated. To ascertain the subsequent course of their disease, questionnaires were sent to these patients during the summer of 1958. The questions related to general health, continuation and severity of complaints, and employability as assessed by the patients themselves. The purpose of this article is to report the results of this follow-up study.

One hundred forty-two questionnaires were returned; in addition, nine reports of patients who had died were received. The duration of the disease in the 142 patients who were alive and their employability are indicated in Table 1. It is seen that in the majority (103) the disease was of 10 to 20 years' duration, and that most patients who were employed (80) had had rheumatoid spondylitis for from 10 to 20 years.

Table 1

Duration of Disease (In Years)

	0–5	5–9	10–14	15–20	21–25	25–30	Total
Working Full-Time	0	8	24	11	4	0	47
Working Part-Time	1	3	25	20	2	4	55
Not Working	1	5	12	11	4	7	40
Totals	2	16	61	42	10	11	142

The number of patients who were fully or partially employed and those who were totally incapacitated are indicated in Table 2. This table also indicates the number of patients who received one or more courses of deep x-ray therapy, and those who did not receive x-ray therapy during the course of management of their disease. This was done in an attempt to ascertain whether there was any correlation between the duration of remission of the disease and the intensity of deep x-ray therapy. It is to be remembered that the patients who were given deep irradiation had more active and severe

* Received for publication May 23, 1960.

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TABLE 2
X-ray Therapy

	One Course	Two Courses	Three Courses	Physical Therapy	Total
Working Full-Time	22	7	2	16	47
Working Part-Time	31	8	1	15	55
Not Working	18	7	3	12	40
Totals	71	22	6	43	142

disease than did those who were not given deep x-ray therapy. Of the 47 patients who were well enough to be employed full-time, 16 (36%) did not have irradiation.

The relation of age in decades to employability is indicated in Table 3. The greater number of the fully or partially employed (84) were in the fourth and fifth decades, usually considered to be the most productive years in the life of the majority of individuals.

TABLE 3
Age of Patients

	20–30	31–40	41–50	51–60	61–70	Total
Working Full-Time	9	28	7	3		47
Working Part-Time	1	29	20	4	1	55
Not Working	5	14	9	2	10	40
Totals	15	71	36	9	11	142

The patients' own evaluation of the severity of their complaints is indicated in Table 4. It is seen that 41 had mild or no complaints, 83 stated that their complaints were of the same severity, and 18 had more severe complaints.

DISCUSSION

The limitations of the methods employed in this study are obvious, and the difficulties encountered in attempts to ascertain employability via questionnaires in a group of individuals are well known. It was particularly

TABLE 4
Complaints

	None or Milder	Same	More Severe	Total
Working Full-Time	27	18	2	47
Working Part-Time	11	38	6	55
Not Working	3	27	10	40
Totals	41	83	18	142

disconcerting that, of the 267 inquiries, only 142 plus nine replies (57%) were received. It is significant, however, that of the 142 patients who replied to the questionnaires, 102 (72) were partially or fully employed. Hart,[2] in a similar study of 200 patients with rheumatoid spondylitis, found that 80% were fully employed and an additional 8% were partially employed. Blumberg and Ragan,[3] in a follow-up study of 121 patients, found that 92 (76%) were fully employed, and that an additional 11 (9%) were partially employed. Of 196 patients studied by Wilkinson and Bywaters,[4] 153 (78%) were fully employed, and an additional 29 (14%) were partially employed. We have no satisfactory explanation to offer for the difference in employability between the groups of patients of these investigators and the group in this study, except to suggest the consideration that all of our patients were veterans, many of whom received partial or total disability compensation from the government. The deterrent effect of monetary gain to be derived from alleged or real incapacity on the employability of an individual is well recognized. An additional consideration is the fact that our patients were generally older men, and their disease was of many years' duration.

Nevertheless, it is gratifying to know that the outlook for patients who have rheumatoid spondylitis is more hopeful than is generally believed. We can therefore assure these patients, with a considerable degree of confidence, that the prognosis of their disease regarding employability, general health, and duration of life is good.

Summary

The results of a follow-up study by means of questionnaire in 142 male veteran patients with rheumatoid spondylitis are presented. The age of the patients, duration of their disease, and the relation of intensity of x-ray treatment to employability are tabulated.

No definite correlation was found between employability and intensity of x-ray irradiation.

Patients with rheumatoid spondylitis in general have a good prognosis with regard to both general health and employability.

Summario in Interlingua

Un studio de controlos subsequente esseva effectuate per medio de un questionario a distribution postal in un gruppo de 267 patientes qui in le passato habeva essite observate e tractate pro spondylitis rheumatoide. Le questiones concerneva le stato de sanitate general, le empleabilitate, e le continuitate del gravamines. Esseva recipite 151 responsas (57%). De istos, novem concerneva patientes qui habeva morite. Inter le 142 patientes vive, 102 esseva empleate a plen tempore o a tempore partial (72%). In le majoritate del casos (103), le morbo habeva un duration de inter 10 e 20 annos, e le parte major (80) del numero de patientes in empleo total o partial habeva habite spondylitis rheumatoide durante inter 10 e 20 annos. Octanta-quatro del empleatos total o partial habeva etates de inter 30 e 50 annos. Quaranta-un pa-

tientes reportava que illes habeva nulle o solmente leve gravamines; 83 reportava que lor gravamines esseva ancora del mesme grado de severitate; 18 reportava que lor gravamines esseva plus sever. Le analyse del effectos de roentgenotherapia profunde o de su grado de intensitate super le empleabilitate del patiente revelava nulle definite correlation.

Le resultatos de iste studio indica que le prospectos pro patientes con spondylitis rheumatoide es melior que lo que es generalmente credite e qui il es justificate assecurar iste patientes con grados considerabile de confidentia que le prognose pro lor morbo es bon con respecto al empleabilitate, al stato de sanitate general, e al longevitate a expectar.

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STRING IMPREGNATION TEST ("STRING TEST") FOR LESIONS OF THE UPPER DIGESTIVE TRACT *

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DIAGNOSTIC capabilities regarding diseases of the esophagus, stomach and small intestine have greatly broadened since the development of the technics of radiology, gastroscopy, esophagoscopy and, more recently, blind biopsy. Despite these refinements, however, certain information concerning lesions of these organs continues to elude the clinician.

Tumor, ulcer, and deformity located distal to the gastric pylorus are inaccessible to the gastroscopist and must be identified by radiologic methods. Diagnosis of certain superficial disturbances, such as esophagitis and gastritis, may be verified only by endoscopic and blind biopsy technics. Erosive and certain ulcerative lesions which lie distal to the gastric pylorus cannot be visualized by present endoscopic and radiologic technics because of their small size or difficult position, and may be missed altogether.

Mucosal lesions of the upper digestive tract, capable of producing significant hemorrhage, may not be apparent radiologically, and may not be seen endoscopically because of anatomic inaccessibility, or because the endoscopic approach is not available.

In certain instances of peptic ulcer of the duodenum, organ irritability and bulb deformity thwart radiologic attempts to demonstrate the ulcer niche. For the same reason, multiple ulcers may be missed.

There are occasions when the physician entertains only a borderline suspicion of an upper digestive tract lesion, and may be reluctant to recommend an upper gastrointestinal series, much less an endoscopic examination, which might appear to the patient to be more formidable than his disease.

In the follow-up management of peptic ulcer of the duodenum, economic considerations and an ever-increasing preoccupation with the cumulative effects of diagnostic irradiation may restrain the physician from requesting a radiologic evaluation of organ response to his prescribed therapy.

The lesions of the upper digestive tract mucosa mentioned above have a common factor, namely, that variable amounts of blood are released into the digestive tract, often in the absence of radiologic abnormality, and sometimes even in the absence of a positive test for occult blood in the feces.

* Received for publication June 8, 1960.

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Presented in part before the Regional Meeting of The American College of Physicians for the District of Columbia and Maryland at The Johns Hopkins Hospital, Baltimore, Maryland, November 7, 1959.

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The potential utility of a simple, convenient and informative diagnostic test of the integrity of the upper digestive tract mucosa is apparent.

A modification of the thread impregnation test of Einhorn [1-6] offers promise of meeting this need in part. In this procedure, the subject swallows the weighted end of a piece of soft cotton string or narrow umbilical tape 100 or more centimeters long. The free end is taped to the cheek and the string is allowed to remain in the upper digestive tract overnight. The following morning, the string is withdrawn and inspected for stains of blood and bile. Location of a bleeding area may be inferred from the distance between the blood stain and the lips. String segments from 15 to 40 cm. from the lips are considered to be esophageal; those from 40 to 55 to 60 cm., gastric; and those beyond 55 to 60 cm., duodenal and jejunal in sequence.

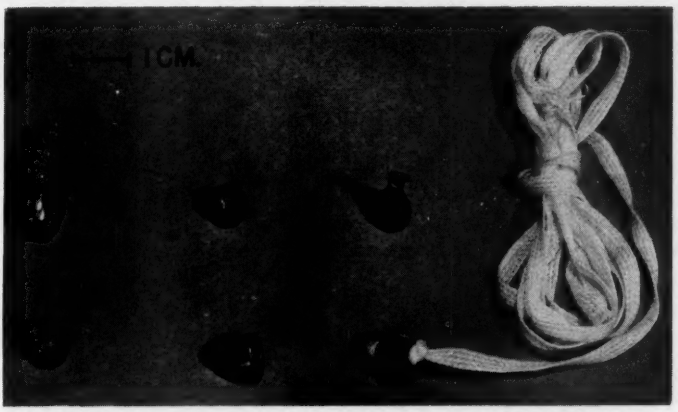

FIG. 1. Assortment of objects used to weight the string for swallowing. Weights smaller than the one shown attached to the tape sometimes failed to traverse the duodenum. The largest weight (X) was too large for easy withdrawal.

The clinical study reported here was carried out in an attempt to evaluate this simple procedure as a diagnostic aid in the study of the upper digestive tract.

MATERIAL AND METHODS

Preparation of Strings: The string used was of soft cotton, 2 mm. in diameter and 100 to 110 cm. long, or was narrow cotton umbilical tape of similar length. A suitable weight was affixed to one end (Figure 1). A simple knot was tied 10 cm. from the free end to serve as a reference point.

Methods: Each string was swallowed in the evening between five and nine o'clock without preliminary preparation of the subject except for an explanation of the procedure. The string was moistened with water for comfort. The subject was then instructed to swallow the weighted end of the string. Increments of from 10 to 15 cm. of string were swallowed with

sips of water during a period of several minutes thereafter until the reference knot reached the lips. The impulse to gag was suppressed by deep mouth breathing. The oropharynx was inspected to verify that the string had not collected there. If necessary, redundant string was withdrawn and then reswallowed. The free end of the string was fastened to the cheek with adhesive tape. The subject was then allowed a normal routine of activity, without precaution or restriction so far as the string was concerned.

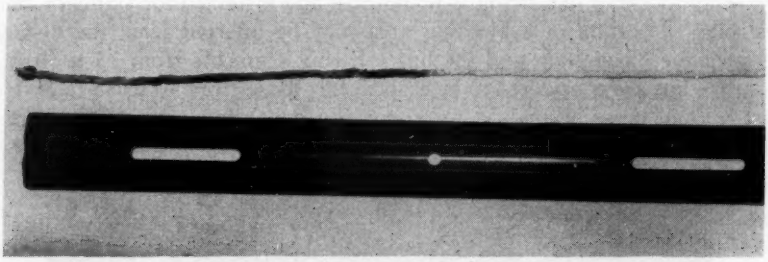

FIG. 2. A 3-plus blood stain localized to the duodenal string segment.

A scout roentgenogram of the abdomen was taken at eight o'clock the following morning to record the location of the weighted end of the string. The string was then gently withdrawn. Occasionally the lead ball stopped at the oropharynx. In this event, the subject was instructed to gag or swallow and the weight was easily withdrawn. After removal, the string was inspected for stains. Deep bile discoloration of the distal end was found to be a reliable index of duodenal entry. Visible blood deposits ranged from very faint stains to heavy clots of gross blood.

The string was laid out lengthwise on a strip of paper toweling, and a freshly prepared guaiac test solution (knife point of guaiac plus 2 c.c. each of 95% ethyl alcohol and 3% hydrogen peroxide) was applied dropwise along its length. Blue color reaction was noted. Blood deposits were graded from 1- to 4-plus according to the following criteria:

STRING TEST CRITERIA

String Test Result	Blood Stain	Guaiac Test
Negative	None visible	Negative
1-plus	None visible	Positive
2-plus	Light, superficial	Positive
3-plus	Penetrating	Positive
4-plus	Gross blood clot	Positive

Figure 2 shows a string bearing a 3-plus blood stain.

Clinical Material: Subjects were patients who were hospitalized at the U. S. Army Hospital in Augsburg, Germany, and at the University and Mercy Hospitals in Baltimore, Maryland, and also included University of Maryland senior medical students. A total of 206 subjects was tested.

Radiologic examination of the upper digestive tract was carried out within several hours of string removal in each instance except for 14 subjects

in whom the weighted string did not enter the duodenum on the first trial. The radiologist performed the examinations without prior knowledge of the string test results. Most of the films were reviewed by internist and radiologist together.

Results

The results in nine groups of subjects which were recognized during this period are shown in Table 1.

Table 1

Results of the "String Test" in Patients with Lesions of the Upper Digestive Tract (by Groups)

Diagnosis (by Groups)	Number of Subjects and Results					
	Neg.	1-plus	2-plus	3-plus	4-plus	Total
A. Esophagitis	0	4	6	1*	0	11
B. Acute gastritis	3	9	2	0	0	14
C. Active duodenal ulcer, uncomplicated	2	1	15	53	16	87
D. Duodenal abnormality without definite ulcer niche	1	2	13	15	3	34
E. Esophageal hiatus hernia						
1. Esophageal stain	1	0	9	5	1	16
2. Duodenal stain	14	0	1†	1‡	0	16
F. Peptic ulcer at gastrojejunal stoma	0	0	0	3	0	3
G. Gastric ulcer	0	0	2	6	0	8
H. Prolapse of gastric mucosa	0	3	3	1	0	7
I. Radiologic normals	21	2	1	2	0	26

* Esophageal ulcer.
† Deformed duodenum.
‡ Duodenal ulcer niche.

Group A: Esophagitis

Eleven subjects were considered to have acute esophagitis associated with recent (within hours) regurgitation or vomiting and a retrosternal burning sensation. Radiologic examination was normal for each subject except one, in whom an esophageal ulcer was identified. String test results are shown in Table 1, A. The blood stains were diffuse in distribution and were pregastric in location.

Group B: Acute Gastritis

Fourteen subjects had upper gastrointestinal symptoms associated with acute gastroenteritis and acute gastritis (food poisoning, acute alcoholism, one case of oil of wintergreen ingestion). Radiologic examination was normal in each instance. String test results are shown in Table 1, B. Only two subjects showed grossly visible light blood stains. Stains were diffuse and were distributed over gastric and duodenal string segments.

Group C: Active Duodenal Ulcer, Uncomplicated

Eighty-seven subjects were found to have a definite ulcer niche of the duodenum by radiologic examination. String test results are shown in

Table 1, C. All but three subjects showed grossly visible blood stains. Each blood stain in this group was localized to a duodenal string segment from 2 to 6 cm. long.

Group D: Duodenal Abnormality Without Definite Ulcer Niche

Thirty-four subjects were found to have radiologic evidence of a duodenal abnormality such as bulb deformity, irritability, and irregular mucosal pattern. A definite ulcer niche was not demonstrated. String test results are shown in Table 1, D. All but three subjects showed grossly visible blood stains. As in the group of subjects with demonstrated duodenal ulcer niche, blood stains in this group were localized to duodenal string segments from 2 to 6 cm. long.

Group E: Esophageal Hiatus Hernia

Fourteen subjects with symptomatic esophageal hiatus hernia were tested. Complaints were of regurgitation, retrosternal burning, nausea, and occasional vomiting, all aggravated by recumbency after eating. One of the subjects also complained of mid-epigastric boring hunger pain, relieved by food or milk. Radiologic examination demonstrated a sliding esophageal hiatus hernia in each instance. A deformed duodenum in one subject and a duodenal ulcer niche in another were additional radiologic findings. String test results are shown in Table 1, E. All but one subject showed grossly visible esophageal segment blood stains. Two subjects also showed grossly visible duodenal segment blood stains. Thus, in two of these subjects, two lesions were detected by the string test technic.

Group F: Peptic Ulcer at Gastrojejunal Stoma

Three subjects had peptic ulcer at a gastrojejunal stoma. All were Caucasian males, from 29 to 44 years of age, admitted to the hospital because of massive bleeding following subtotal gastric resection two to four years earlier. The presence of stomal ulcer was established by radiologic and gastroscopic examinations. String test results are shown in Table 1, F. Grossly visible blood stains were noted in each instance. The blood stains were localized to string segments from 6 to 8 cm. long, and began from 48 to 56 cm. from the reference knot.

Group G: Gastric Ulcer

Eight subjects with gastric ulcer by radiologic and gastroscopic examinations were tested. One ulcer later proved to be malignant. String test results are shown in Table 1, G. All showed grossly visible gastric segment blood stains. The blood stains, brownish in color, were localized to gastric string segments from 2 to 8 cm. long. One of the subjects had radiologic findings of a lesser curvature antral gastric ulcer associated with nondiagnostic radiologic changes in the pars media. The string test showed

two blood deposits: one, a 2-plus stain on the antral segment; the other, a 3-plus stain on the proximal pars media segment. Gastroscopic examination revealed the presence of two closely spaced, active gastric ulcers situated on the anterior wall of the proximal pars media near the lesser curvature. The antral ulcer was not seen gastroscopically because of its anatomic inaccessibility.

Group H: Prolapse of Gastric Mucosa

Radiologic changes of prolapsed gastric mucosa were found in seven subjects. String test results are shown in Table 1, H. Four of the seven subjects showed grossly visible blood stains. Each blood stain was localized to a pyloroduodenal string segment from 2 to 3 cm. long.

TABLE 2

Duodenum Evaluation—Summary

String Test	No.	Radiologic Findings			
		Negative	Niche	Correlation	Abnormality W/O Niche
Negative or 1-plus	83	77	3	3.6%	3
2-plus	30	1	15	50%	14
3-plus	71	2	54	76%	15
4-plus	19	0	16	84%	3
Total	203	80	88		35

Group I: Radiologic Normals

There were 26 symptom-free subjects with negative radiologic examination. String test results are shown in Table 1, I. Three of the subjects showed grossly visible duodenal segment blood stains. The blood stains were localized to the duodenal string segments.

CORRELATION

Abnormalities of the duodenum were the lesions most frequently encountered during the study. Table 2 summarizes the string test results and radiologic findings of 203 subjects whose data permitted correlation of duodenal evaluation by the two methods. It may be noted that 2-, 3- and 4-plus duodenal segment blood stains were associated with the radiologic demonstration of duodenal ulcer *niches* in 50, 76 and 84% of the subjects, respectively. Only 3.6% of 83 subjects with negative or 1-plus duodenal segment blood stains showed duodenal ulcer niches radiologically. Two of these patients were explored surgically and no duodenal ulcer was found, reducing the false-negative string test incidence to 1.2% or less as far as radiologically demonstrated ulcer niche is concerned.

Consideration of the data may be simplified by designating string test

results as positive or negative, based upon the presence or absence of *grossly visible* blood staining of the duodenal string segment, and by designating radiologic findings as positive or negative for evidence of duodenal disease, based upon the presence or absence of deformity and spasticity, with or without ulcer niche demonstration.

Radiologic findings then correlate with string test results as shown in Table 3. It is noted that 83 subjects had negative string tests (no grossly visible blood staining of the duodenal string segment). Seventy-seven of these subjects also had negative radiologic studies, a correlation of 93% between negative string test results and negative radiologic findings. Of the 120 subjects with positive string test results (grossly visible blood staining of the duodenal string segment), 117 also had radiologic findings indicative of duodenal disease, a correlation of string test results with radiologic findings of 97%.

TABLE 3

String Test vs. Radiologic Duodenum Evaluation

String Test	No.	Radiologic Findings		
		Negative	Positive	Correlation
Negative	83	77	6	93%
Positive	120	3	117	97%
Total	203	80	123	

Clinical interpretation of "duodenal abnormality without ulcer niche," noted radiologically, required individualized evaluation. It appears likely that some of the subjects with this finding actually had active ulcers which were not demonstrated radiologically. This likelihood is supported by the 3- and 4-plus blood stains noted on the duodenal segments of strings recovered from many of these subjects (Table 2).

The frequency with which 1- and 2-plus duodenal blood stains were encountered suggests that the string or tape itself abraded the duodenal mucosa to evoke the light blood stains. Such string-induced irritation might similarly be suspected of causing the duodenal irritability and spasticity noted during subsequent radiologic examination of these subjects. In some subjects, a high degree of motor activity involving areas exposed to the string, notably the distal esophagus and the gastric pylorus, might cause mucosal abrasion and blood stains.

String-test results correlate with radiologic findings, as shown in Table 4. Eighty subjects had negative radiologic examination for evidence of duodenal disease. Seventy-seven of these also had negative string tests (no grossly visible blood staining of the duodenal string segment), a correlation of 96% between negative radiologic findings and negative string-test results. Of the 123 subjects with radiologic findings indicative of duodenal disease,

117 also had positive string-test results (grossly visible blood staining of the duodenal string segment), a correlation of 95% between positive string-test results and radiologic findings indicative of duodenal disease.

Two subjects were admitted to the hospital because of recurrent massive gastrointestinal hemorrhage. Repeated radiologic examination had been negative in each case. String test in each of these patients showed grossly visible (3-plus) blood staining of the duodenal string segment. Surgical exploration disclosed the presence of an active duodenal ulcer in each of these patients.

Another subject had suffered an episode of massive hematemesis and melena seven weeks earlier. He had never noticed symptoms referable to peptic ulcer. Two string tests were negative. X-ray examination demonstrated a deformed duodenum. Because this was the second episode of

TABLE 4

Radiologic vs. String Test Duodenum Evaluation

Radiologic Findings	No.	String Test		
		Negative	Positive	Correlation
Negative	80	77	3	96%
Positive	123	6	117	95%
Total	203	83	120	

severe bleeding for this patient, an abdominal laparotomy was performed. The duodenum was found to be bound down and deformed by firm adhesions. No ulcer crater was found.

DISCUSSION

The procedure was found to be quite simple, generally applicable, and free of complication. The factor which most determined successful introduction of the weighted string was the physician's attitude. A combination of authority, patience, sympathy, and matter-of-factness was almost always successful. The offer of the string by a hospital attendant or by a disinterested physician or nurse frequently was unsuccessful. An art of "talking the string down" was recognized during the study.

It was not possible to establish from the location of the weight opacity on the abdominal scout roentgenogram whether the string had entered the duodenum. The presence of bile stain on the distal end of the string, however, was found to be a reliable index of duodenal entry.

A satisfactory weight was found to be a 0.8 cm. lead ball having a central hole and weighing 2.2 to 2.5 gm. This was easily swallowed and withdrawn.

To trace the course of the string radiologically, early in the study five or six smaller lead weights were affixed to several of the strings at various

points (Figure 3). Each of these strings, when withdrawn, showed 3- to 4-plus blood stains immediately adjacent to the guide weights. Localization of these stains next to the extra weights clearly indicated traumatic bleeding, and this practice was discontinued. For this reason, blood stains sometimes noted next to the distal weight were disregarded.

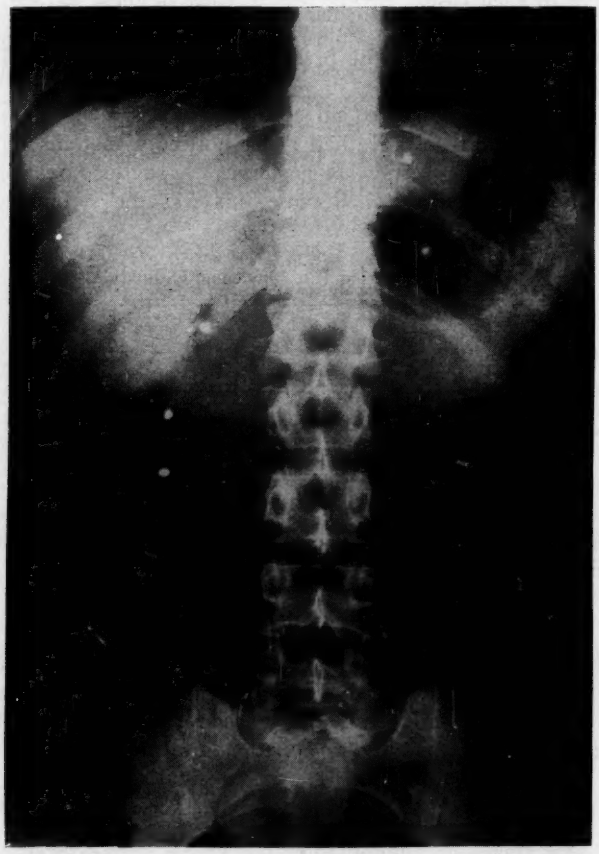

FIG. 3. Abdominal scout roentgenogram, showing opacities of multiple weights attached at intervals along the string. The duodenal loop is readily identified. The extra weights traumatized the mucosa, and this technic was discontinued.

More precise localization of a bleeding site was achieved by the use of a modified tape marked with a longitudinal strip of opaque material and crossed with similar material at regular intervals. A scout roentgenogram of the abdomen, taken after the tape was swallowed, revealed the outline of the upper digestive tract coursed by the opacified material (Figure 4). Such opacified tape has also been used in conjunction with intravenous

fluorescein dye injection to localize currently bleeding lesions of the upper digestive tract.[7] In the presence of active bleeding, the fluorescein dye impregnates the swallowed tape along with the fresh blood. The recovered tape is then inspected for fluorescence under an ultraviolet light source. One

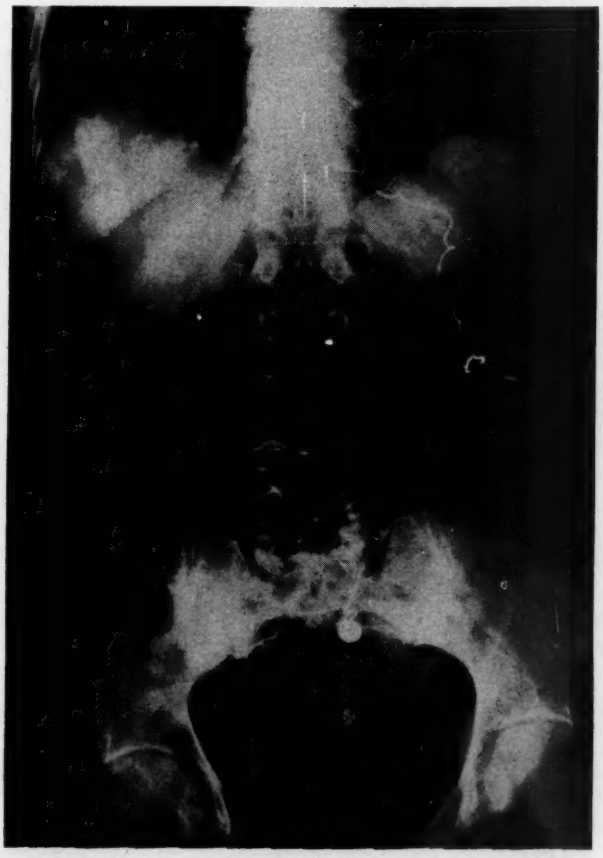

FIG. 4. Abdominal scout roentgenogram, showing an opacified tape in situ. Opaque cross-hatches can be identified. With such a film for reference, the anatomic localization of a blood stain is relatively simple.

can visualize the use of other dyes or suitable radioactive isotopes in a similar manner.

Confusion caused by reddish stains of substances other than blood—such as beets, red candies, cherries, jelly, gelatin dessert, grape juice, tomatoes and chocolate—may be avoided by insuring that subjects do not ingest anything other than water during the test, and by applying guaiac test solution to suspected stains.

Since the string itself may abrade the mucosa so that a blood stain results, the possibility of false-positive results should be recognized. False-*negative* results would appear to be less likely, so that negative string tests probably denote the *absence* of mucosal disease more accurately than 1- and 2-plus

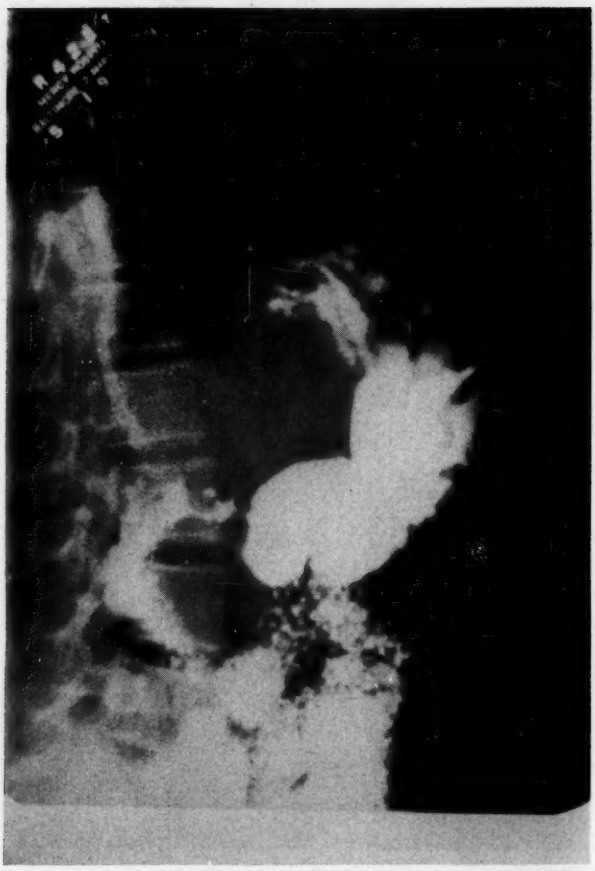

FIG. 5. Roentgenogram taken during upper gastrointestinal series. Radiologic diagnoses: duodenal ulcer and nondiagnostic gastric abnormality. Two string tests were negative. At surgery, no ulcer was found. Examination of tissue sections of the resected stomach disclosed the presence of metastatic carcinoid tumor.

string tests denote the *presence* of active mucosal disease. Any such difference in accuracy between negative and positive string tests may be expected to decrease as the intensity of the blood stains increases. This conclusion is supported by the progressively higher correlation of the heavy 3- and 4-plus blood stains with radiologically demonstrated active mucosal disease (Table 2).

It should be pointed out that, except for subjects who underwent operation or endoscopic examination, radiologic findings necessarily provided the base line from which the presence or absence of mucosal disease was estimated. Such mythical infallibility of the radiologic method in this area certainly must falter before the challenge of such lesions as the diminutive ulcer niche, mucosal erosion, and mucosal superficial inflammation. With these lesions, one rather expects to find light blood staining of swallowed strings, despite associated normal radiologic findings. In such instances the clinician may find new confidence in his own evaluation of the symptomatic patient whose upper gastrointestinal series is reported to be normal but whose symptoms subside under antacid therapy. Perhaps fewer diagnoses of "purely functional" disease will result if patients can be shown by the string test to have friable, ready-bleeding, or eroded upper digestive tract mucosa.

Conclusions

From the foregoing data, it appears that the string test technic permits detection and localization of active ulceration and erosion of the upper digestive tract with desirable accuracy. The technic has features of simplicity, convenience, benignity, and economy. It may be applied readily on an outpatient basis; the appropriately instructed patient takes the weighted string home for evening swallowing, and delivers or mails the recovered string to the physician the following morning. There need be no loss of time from work. The test should prove especially helpful as a screening procedure for evaluation of the upper digestive tract, and as a method of following the course and progress of duodenal peptic ulcer.

Of great importance is the feature that it may spare patients the cumulative effects of diagnostic irradiation currently applied in the follow-up management of patients with duodenal peptic ulcer.

In some instances the string test detected duodenal disease, later shown surgically, when the radiologic examination was negative.

In other instances the clinician may find confirmation of his suspicions of upper digestive tract disease despite normal radiologic findings when the string test is positive and the patient's symptoms subside under appropriate therapy.

A negative string test may be considered to be strong presumptive evidence that there is no ulceration of that portion of the digestive tract coursed by the string. Thus, a negative string test in a patient with evidence of gastrointestinal bleeding indicates that the bleeding arises from a point in the digestive tract distal to the end of the string, or that a higher lesion has closed over.

Only grossly visible blood stains should be regarded as positive. The heavier the blood stain, the greater the likelihood of demonstrable ulcerative disease of the adjacent mucosa.

We now use a four-foot string routinely.

Summary

Certain erosions and ulcerations of the upper digestive tract continue to escape clinical detection, despite advances in the technics of radiology, gastroscopy, esophagoscopy, and blind biopsy. Failure to detect such lesions results in part from anatomic inaccessibility or technic inavailability in the case of endoscopy; from anatomic inaccessibility or lesion superficiality in the case of radiology; and from capsule placement errors in the case of blind biopsy.

Recognizing the potential value of a simple screening test for the integrity of the upper digestive tract mucosa, the author attempted to evaluate a string impregnation test ("string test"), modified after the technic of Einhorn, for mucosal lesions of this area.

Each of 206 subjects swallowed the weighted end of soft cotton string or narrow umbilical tape, 100 to 110 cm. long. The free end was taped to the cheek and the string was allowed to remain in place overnight. The string was withdrawn the following morning and was then examined for stains of blood and bile. The distances of such stains from the lips were measured. Each string test was correlated with an upper gastrointestinal series radiologic examination performed shortly after string removal. Conditions present during the string tests of 206 subjects included acute esophagitis, acute gastritis, active duodenal ulcer niche, duodenal abnormality without niche demonstration, esophageal hiatus hernia, gastrojejunostomy stomal ulcer niche, gastric ulcer, prolapse of gastric mucosa, and radiologically normal upper digestive tract.

The presence of grossly visible blood stains on the recovered string was found to be an accurate indication of erosion or ulceration of contiguous mucosa. Some false-positive results occurred with lighter stains. The heavier the blood deposit, the more likely was there to be associated demonstrable mucosal disease. Negative string tests very accurately indicated normal contiguous mucosa. Deep bile discoloration of the distal end of the string was found to be a reliable indication that the string had passed into the duodenum.

From the correlated findings of string tests and upper gastrointestinal series radiologic examinations, the author concludes that the string test technic permits detection and localization of active ulceration and erosion of the upper digestive tract with desirable accuracy. The technic is simple, convenient, economical, and without complication. It can be used as a screening test and for the follow-up evaluation of upper digestive tract lesions. Particularly, it can spare patients the cumulative effects of x-ray irradiation applied in the follow-up management of duodenal peptic ulcer.

Acknowledgement

The author wishes to express his appreciation to Friedrich A. Lingl, M.D., of Columbus, Ohio, for his assistance during the early phase of this study.

Summario in Interlingua

Certe erosiones e ulcerationes del vias supero-digestive continua escappar al detection clinic in despecto del progressos effectuate in le technicas de radiologia, gastroscopia, esophagoscopia, e biopsia cec. Le non-detection de tal lesiones resulta in parte ab le inaccessibilitate anatomic o le non-disponibilitate technic in le caso de endoscopia, ab le inaccessibilitate anatomic o le superficialitate del lesion in le caso de radiologia, e ab errores in le placiamento del capsula in le caso de biopsia cec.

Recognoscente le valor potential de un simple test de orientation pro le integritate del mucosa in le vias supero-digestive, le autor ha tentate evalutar un test a impregnation de corda ("test de corda")—modificate super le base del technica de Einhorn—pro lesiones mucosal in iste area.

Cata un de 206 subjectos inglutiva le ponderate termino de un molle corda de coton o de un fin banda umbilical, de un longor de inter 100 e 110 cm. Le termino libere esseva attachate al gena, e le corda esseva lassate in sito durante le nocte. Le corda esseva extrahite le sequente matino e esseva examinate pro maculas de sanguine e de bile. Le distantias de tal maculas ab le labios esseva mesurate. Omne test de corda esseva correlationate con un serie supero-gastrointestinal de studios radiologic que esseva obtenite brevemente post le extraction del corda. Le conditiones presente in le 206 patientes al tempore del tests de corda includeva esophagitis acute, gastritis acute, niche de acute ulcere duodenal, anormalitate duodenal sin demonstration de niche, hernia de hiato esophagee, niche de ulcere stomal post gastrojejunostomia, ulcere gastric, prolapso de mucosa gastric, e normalitate radiologic del vias supero-digestive.

Esseva trovate que le presentia de grossiermente visibile maculas de sanguine in le extrahite corda esseva un indication accurate de erosion o ulceration in le mucosa contigue. Plure resultatos falsemente positive occurreva con maculas pauco decidite. Quanto plus marcate le deposito de sanguine, tanto plus probabile le presentia concomitante de un demonstrabile morbo mucosal. Resultatos negative del test de corda indicava accuratissimemente un normal mucosa contigue. Un forte discoloration biliar del termino distal del corda se revelava como un indication fidel que le corda habeva passate a in le duodeno.

Super le base del correlation inter le resultatos del test de corda e illos de un serie supero-gastrointestinal de studios radiologic, le autor conclude que le technica del test de corda permitte le detection e localisation de ulceration e erosion active del vias supero-digestive con le desirate grado de accuratia. Le technica es simple, convenibile, economic, e libere de complicationes. Illo pote esser usate como test de orientation e in le evalutation de controlo posterior in casos de lesiones del vias supero-digestive. In particular, illo pote evitar pro le patiente le effectos cumulative de irradiation roentgenoscopic in le tractamento de continuation de ulcere peptic del duodeno.

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PULMONARY EOSINOPHILIC GRANULOMA: A CLINICAL AND PATHOLOGIC DISCUSSION *

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INTRODUCTION

IN 1953 Lichtenstein [1] proposed the name "histiocytosis X" to designate the three related disease complexes, Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma of bone. This term was chosen in order to integrate the three diseases under a single descriptive heading and to emphasize their basic pathologic process, that of histiocytic proliferation in the particular tissue involved. Lichtenstein's terminology climaxed a period during which pathologists investigating these diseases expressed the opinion that eosinophilic granuloma of bone, as originally described by Otani and Ehrlich [2] and by Lichtenstein and Jaffe [3] in 1940, was one variation in the clinical expression of a single disease, the other forms being Schüller-Christian disease and Letterer-Siwe disease.[4-6] Since 1953, the use of the term histiocytosis X has been generally adopted as Lichtenstein proposed, even though the older and probably better known names are still employed.

Among the many clinical manifestations of histiocytosis X, pulmonary involvement has often been recognized. Pulmonary lesions have been described at autopsy in a number of cases of disseminated histiocytosis X.[7-12] In addition, abnormal chest roentgenograms (usually described as showing "diffuse fibrosis") have been seen in patients with disseminated lesions, with proof of the disease established in biopsies from other involved organs.[13-17] It was not until 1951, however, that Farinacci et al.[18] reported two cases apparently with pulmonary lesions alone. The facts that the lungs were the only organs seen to be involved and that the diagnosis was made by lung biopsy made this circumstance unique. Since then there have been a number of similar reports in the literature. We have found 40 such cases where pulmonary lesions were found with the histiologic features, in lung biopsies, as described in eosinophilic granuloma of bone.[19-36] Biopsy was done usually as a purely diagnostic procedure, but was performed in several cases at the time of thoracotomy for recurrent pneumothorax. Cases in which evidence of other organ involvement was present are included in this

*Received for publication May 13, 1960.

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review, as long as proof (lung biopsy) of pulmonary involvement was offered.

In this discussion, five additional cases of eosinophilic granuloma involving the lungs will be presented. All of these patients were seen and diagnosed during a six-month period in 1958. Since that time, no other proved case has been encountered in our hospital. Following the case reports, we will analyze certain features in this disease, as seen in the 45 cases, to clarify further the clinical and pathologic picture.

Case Reports

Case 1. A 29-year-old white male was admitted to the hospital on January 27, 1958. A routine chest roentgenogram taken in November, 1957, had been found to be abnormal. The patient had no symptoms, and specifically denied all pulmonary complaints.

A complete physical examination revealed no significant abnormalities. A previous chest roentgenogram, dated January, 1957, was reviewed and this film was within normal limits. Routine laboratory studies showed a normal blood count and urinalysis. Peripheral eosinophilia was not noted. The sedimentation rate was normal, and complement fixation tests for histoplasmosis, coccidioidomycosis, and blastomycosis were negative. An intermediate strength PPD (0.0001 mg.) gave a 3-plus reaction. Liver function tests were normal. The chest roentgenogram dated January, 1958, showed diffuse nodular infiltrates in all lung fields, with a tendency toward confluency in some areas. Multiple small radiolucencies were scattered throughout. Hilar shadows were normal. A complete bone survey was negative.

Prior to the patient's admission to Valley Forge General Hospital, a diagnosis of pulmonary tuberculosis had been made and he had been given isoniazid and streptomycin therapy. A right prescalene lymph node biopsy had also been performed and was negative. Tuberculosis was not proved by culture, and the chest roentgenograms seemed rather atypical for this disease. For this reason, a lung biopsy was performed on March 17, 1958. The patient withstood the procedure well, and the postoperative course was uneventful. Pathologically, the resected specimen showed changes compatible with a diagnosis of pulmonary eosinophilic granuloma.

Following establishment of this diagnosis, the patient was given oral cortisone, 300 mg. daily for 10 weeks. Serial chest roentgenograms showed no real change. A course of radiation therapy was then given, the patient receiving a total dose of 1,600 r to two anterior and two posterior fields. A chest roentgenogram taken two months after completion of radiation therapy again showed little change. The patient was released from the hospital in July, 1958, and continued to be asymptomatic. A subsequent chest roentgenogram in June, 1959 showed no change.

Case 2. A 21-year-old white male was hospitalized in December, 1957, because of an abnormal chest roentgenogram detected during routine screening procedures. His only symptom was a mild, nonproductive cough during the two months preceding hospitalization. Previous chest roentgenograms were not available for comparison. Films taken in November and December, 1957, showed small, nodular infiltrations scattered throughout all lung fields, with coalescence of these nodulations in some areas. There were many small, thin-walled cystic areas that measured from 0.5 to 1.0 cm. in diameter. There was no hilar enlargement or evidence of pleural effusion.

Physical findings were entirely within normal limits. Routine laboratory work, which included a complete blood count, urinalysis, and serologic test for syphilis, was negative. There was no eosinophilia. Histoplasmin skin test (histoplasmin antigen in a 1 : 100 dilution) was weakly positive. Intermediate strength PPD (0.0001 mg.)

and second strength PPD (0.005 mg.) were both negative. Liver function tests were within normal limits, and a complete bone survey was negative for osseous lesions. A liver biopsy was performed and the tissue showed no abnormality. An open thoracotomy and a diagnostic lung biopsy were done on February 12, 1958. The specimen showed the histologic changes of eosinophilic granuloma involving lung tissue.

The patient's postoperative course was uneventful. He was placed on oral cortisone therapy, 300 mg. daily in divided doses for a period of 10 weeks. The chest roentgenogram showed no significant clearing. He was discharged from the hospital in June, 1958, and was asymptomatic at this time. There has been no follow-up.

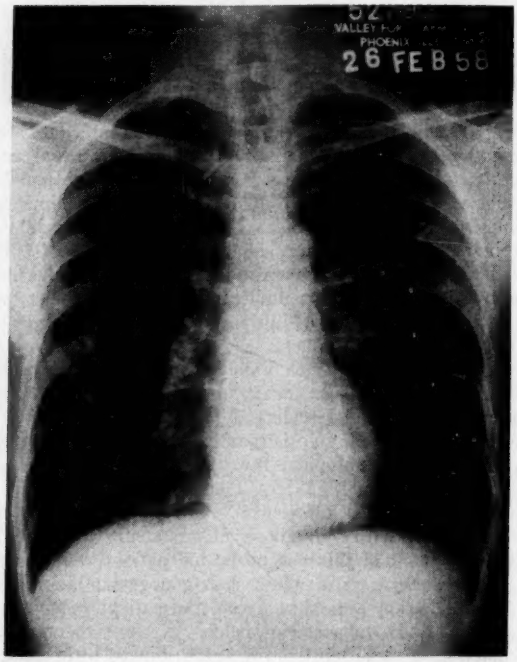

FIG. 1. *Case 4.* Chest film, taken on February 26, 1958, before lung biopsy. The diffuse, nodular character of the process is shown, as well as the cystic appearance.

Case 3. A 21-year-old white male was admitted to the hospital on May 23, 1958. A routine chest roentgenogram taken one month previously had been found to be abnormal. A chest film in July, 1957, had been within normal limits. The patient admitted to having had a chronic, nonproductive cough for a number of months. He denied all other pulmonary complaints, and was otherwise entirely without symptoms.

A complete physical examination was negative. A chest roentgenogram dated May, 1958, showed diffuse linear and nodular densities throughout both lung fields. There were numerous areas of radiolucency, suggesting cyst formation. These measured from 0.5 to 1 cm. in diameter. The hilar structures were normal, and pleural effusion was not seen. Films of the long bones and skull were negative. Routine laboratory work included a complete blood count, urinalysis, and liver func-

tion tests, and all were normal. There was no peripheral eosinophilia. The intermediate strength PPD (0.0001 mg.) and fungus skin tests were negative.

On June 23, 1958, an open thoracotomy and a diagnostic lung biopsy were carried out. The histologic picture of the resected tissue was compatible with a diagnosis of pulmonary eosinophilic granuloma. Following convalescence from surgery, the patient was discharged from the hospital in July, 1958. He was completely asymptomatic, and his chest roentgenogram showed no appreciable difference from that of May, 1958. No follow-up has been obtained.

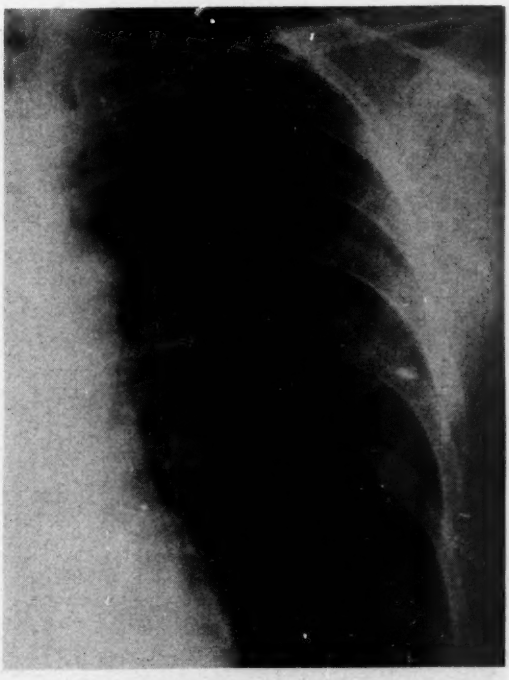

FIG. 2. *Case 4.* This is a magnification of the left midlung field, taken from the February, 1958, film. The nodular infiltrations and the multiple radiolucent areas are emphasized by the enlargement.

Case 4. A 50-year-old white male was hospitalized on February 5, 1958, having been referred with a diagnosis of active pulmonary tuberculosis. A routine chest roentgenogram, taken in February, 1958, had been found to be abnormal, and hospitalization was recommended. The patient denied feeling ill, but did admit to having had mild fatigability and a chronic, nonproductive cough for a number of months.

A complete physical examination revealed no significant abnormalities. Chest roentgenograms taken in February, 1958 (Figures 1 and 2), revealed both discrete and confluent areas of nodulation scattered throughout both lungs, more prominent in the left and right midlung fields. There were multiple areas of radiolucency, measuring from 0.5 to 1.5 cm. in diameter. The hilar structures were not enlarged, and there was no evidence of pleural effusion. The routine initial laboratory work showed no abnormalities. Liver function tests and peripheral eosinophil counts were

normal. A skull film showed a single cystic area, measuring 1 cm. in diameter, in the right parietal area. No other osseous lesions were seen. A liver biopsy specimen was negative.

The patient was asymptomatic during his hospitalization. Following a period of diagnostic investigation, an open thoracotomy and a lung biopsy were carried out on March 10, 1958. The specimen contained scattered nodules that histiologically showed the changes of pulmonary eosinophilic granuloma. The patient did well postoperatively. In April, 1958, oral cortisone therapy was started, in initial doses of 300 mg. daily. This treatment was continued for six weeks. Chest roentgenograms during this period showed gradual clearing of the pulmonary parenchymal infiltration. The patient was discharged from the hospital in June, 1958. No follow-up data are available.

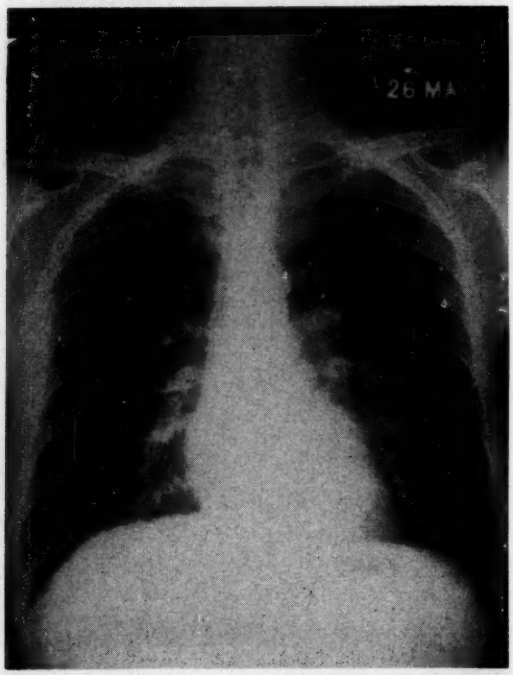

FIG. 3. *Case 5.* Chest roentgenogram, taken in May, 1958, prior to diagnostic lung biopsy. The changes are those of a diffuse reticulonodular infiltration.

Case 5. A 49-year-old white male was first admitted to the hospital on May 16, 1958, because of a 20-pound weight loss, easy fatigability, and the finding of an abnormal chest roentgenogram several weeks previously. The patient had been a moderately heavy smoker for a number of years, and admitted to a chronic, mildly productive cough. He denied dyspnea, orthopnea, hemoptysis, chest pain, or frequent respiratory infections. There was no history of exposure to toxic inhalants, and there was no known contact with tuberculosis or fungus diseases.

On physical examination the patient was a thin male who did not appear to be either acutely or chronically ill. The blood pressure was 140/85 mm. of Hg; pulse,

75; temperature, 98.8° F. The chest was symmetric, with good expansion, and only an occasional expiratory wheeze was heard on auscultation. There were no audible râles. The heart sounds were regular, the tones of good quality, and no murmurs were heard. Examination of the abdomen revealed the liver edge to be palpable two fingerbreadths below the right costal margin. The spleen was not felt. The rest of the physical examination was within normal limits.

Laboratory studies included a normal urinalysis, hematocrit, white blood cell count, and differential count. There was no eosinophilia. Tuberculin skin tests (intermediate and second strength PPD) were negative, as were fungus skin tests.

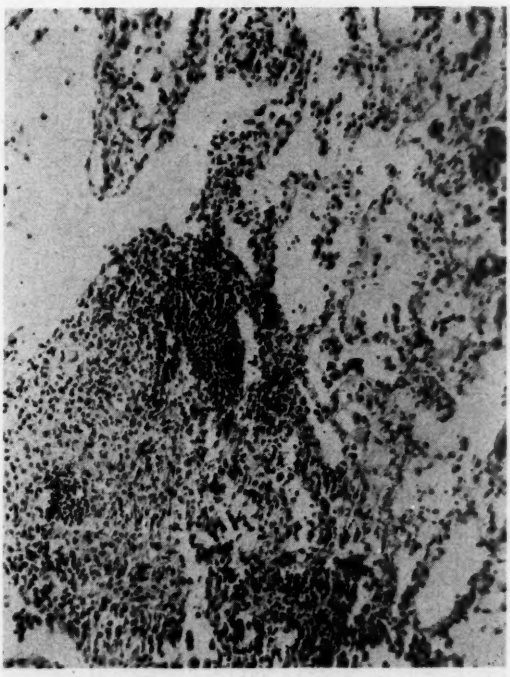

FIG. 4. *Case 5.* Photomicrograph of a section of the lung specimen. The lighter-staining cells are histiocytes, while the accumulation of smaller, dark-staining cells represents eosinophils and lymphocytes. Some histiocytosis of the adjacent alveolar septa is seen.

An electrocardiogram was within normal limits. A chest roentgenogram (Figure 3) revealed diffuse, small nodular infiltrations and a fine reticular pattern throughout both lung fields. These nodulations varied in size from 0.1 to 0.3 cm. in diameter. Both lung fields showed multiple small radiolucent areas, which varied in size from 0.3 to 0.5 cm. in diameter. There was no hilar enlargement or evidence of pleural fluid.

The patient underwent an open thoracotomy on June 13, 1959, for the purpose of obtaining lung tissue for diagnosis. At operation, definite nodulations were palpated on the lung surface. A biopsy was performed, and the patient's postoperative recovery was uneventful. The biopsy specimen (Figure 4) revealed scattered areas of intense granulomatous infiltration composed predominantly of eosinophils and histio-

cytes, with a lesser number of lymphocytes. Some of the histiocytes contained hemosiderin pigment, while others had a somewhat vacuolated, foamy cytoplasm. Adjacent areas of lung parenchyma showed some fibroblastic proliferation, some congestion, and minimal histiocytic invasion of alveolar septa. A few giant cells were seen. Relatively normal lung tissue could be seen interspersed between the areas of granulomatous infiltration.

When the diagnosis of pulmonary eosinophilic granuloma had been made, a complete bone survey was done and was normal. The patient was placed on oral prednisone therapy, initially receiving 40 mg. daily in divided doses, and then being placed on a maintenance dose of 10 mg. daily. He was discharged from the hospital

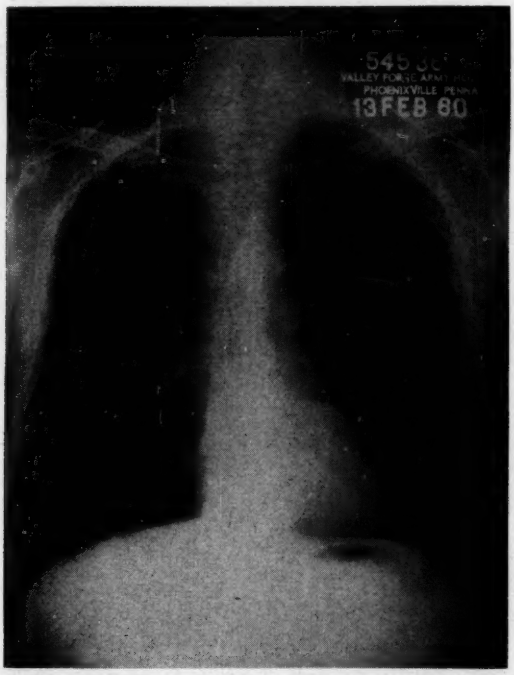

FIG. 5. *Case 5.* Chest film taken in February, 1960. There has been almost complete clearing of the infiltration seen in May, 1958.

on July 28, 1958. Prednisone therapy was continued for approximately 13 months. During this time he noted less fatigability and some return of his vigor. He had no cough or other pulmonary complaints, and slowly regained 15 pounds of body weight.

The patient was rehospitalized in March, 1960, approximately 21 months after the original diagnosis of pulmonary eosinophilic granuloma had been made. A chest roentgenogram at this time (Figure 5) showed definite clearing in comparison with films of May and July, 1958. There was complete disappearance of the nodular lesions, and definite cystic areas could no longer be identified. However, there still seemed to be a fine reticular pattern throughout both lung fields that suggested the presence of residual fibrosis. All routine laboratory data were again within normal

limits. Pulmonary function studies, including lung volume determinations, were carried out, and these will be discussed subsequently.

Discussion

In the recent literature, several different terms have been employed to describe the pulmonary lesion. "Pulmonary eosinophilic granuloma" and "eosinophilic granuloma of the lung" are by far the most commonly used. This is probably the result of the precedent of early terminology. Weiss and Johnston [28] employed the term "pulmonary histiocytosis X," while Nadeau and his associates [36] preferred to use "primary pulmonary histiocytosis X." To employ Lichtenstein's classification, the more detailed term "chronic disseminated histiocytosis X with early extra-skeletal lesions (pulmonary) resembling eosinophilic granuloma" may be used. Whichever terminology is employed, the process referred to is understood to be the same.

Table 1

Presenting Symptoms in 45 Cases of Pulmonary Eosinophilic Granuloma

Symptom	Number
1. No symptoms	7
2. Cough	34
3. Dyspnea on exertion	13
4. Fatigability	9
5. Fever (greater than 100° F.)	4
6. Weight loss	15
7. Chest pain (excluding pneumothorax)	4
8. Hemoptysis (gross)	1

Age, Sex, and Race: Thirty-nine of the patients were male, with an average age of 31 years. The oldest was 59 years of age, the youngest, 15 years of age. There were six female patients, also with an average age of 31 years. All of the patients were Caucasian except for one 42-year-old Negro male. The age and sex distributions are undoubtedly influenced by the fact that 24 of the 45 reported cases have been from military hospitals, tending to include more males of the younger age group. The predominance of the white race has been noted by other authors, but the significance of this observation is obscure.

Symptomatology: An analysis of the presenting symptoms (Table 1) shows that cough is by far the most prominent complaint. It is usually mild and not productive of sputum. Gross hemoptysis is quite unusual, having been noted in only one case. Exertional dyspnea and significant weight loss were noted in less than 50% of the cases. It is of interest that seven of the 45 patients were completely asymptomatic and the disease was detected on routine chest roentgenograms.

The Chest Roentgenogram: The abnormalities found on initial chest roentgenogram have been categorized in Table 2. This breakdown was done on the basis of the author's description of the chest film, as found

in the case reports reviewed. While it is true that this method is inferior to an actual review of all of the films, a fairly specific description of the chest roentgenogram was found in all but four of the cases. In general, the changes could be classified into three groups. As seen in Table 2, the basic lesion appears to be a diffuse nodular type of infiltrate that is both discrete and confluent. Another of the more characteristic changes was the finding of multiple, small radiolucent areas with the appearance of small cysts. The pathologic changes that might account for these areas will be discussed subsequently. A small number of the roentgenograms fell into the other categories, as listed. The one instance where a normal chest film was seen is of some interest. This patient was a 40-year-old man who was found to have an osteolytic lesion in one of his ribs. This was explored surgically and, during the procedure, nodulations were palpated on the lung surface.

TABLE 2

Characterization of the Initial Chest Roentgenogram

Type of Abnormality	Number
1. Diffuse nodular infiltrations, both discrete and confluent	14
2. Above, with reticular pattern	9
3. Diffuse nodularities, discrete and confluent, and multiple small cystic areas throughout	12
4. Predominant linear, "fibrotic" picture with a honeycomb appearance	4
5. Unilateral or bilateral infiltrations, with confluency and a pneumonic pattern	1
6. No definite pattern described	4
7. Normal roentgenogram*	1
Total	45

* Case 1 of May, I. A., Garfinkle, J. M., and Dugan, D. J.[21]

A biopsy was done and the frozen-section report was that of an undifferentiated carcinoma. A lobectomy was performed and sections of the lobe showed changes, not of carcinoma, but of eosinophilic granuloma. A similar histologic picture was found in the rib lesion. One year later, the chest roentgenogram was still negative. The fact that lesions may be present in the lungs and not be detected radiographically would make one wonder how many additional cases of apparently localized eosinophilic granuloma of bone actually are disseminated forms in which this fact is not obvious.

Hilar enlargement was described in two roentgenograms, but at the time of surgery no significant hilar lymphadenopathy was detected. No case was encountered with a pleural effusion.

Other Features: Some of the other clinical features are presented in Table 3. Diabetes insipidus, bone lesions, and spontaneous pneumothorax have all been mentioned by other authors reporting cases of pulmonary eosinophilic granuloma. Our analysis of the 45 cases shows that these findings occur in less than 25% of all cases. Many of the cases had other

biopsy procedures done to demonstrate lesions in other organs. These studies included bone marrow aspirations, prescalene lymph node biopsies, liver biopsy, and excision of other enlarged lymph nodes. In no instance was any helpful information gained from examination of the biopsy material, and in no case could a diagnosis be made by these methods. In addition, many blood serologic tests and chemical tests have been done, and again, no information of a positive nature was obtained. We have closely examined the case reports as to occupation, place of residence, and other factors in the history, but have been unable to discover any facts which might shed some light on the possible etiology of this disease.

Pathology: The gross appearance of the involved lung as seen at thoracotomy was quite similar in all five of our cases. The lung surfaces had a somewhat granular appearance and were nodular to palpation. The microscopic picture was also similar in the five cases. The essential change was that of focal collections of histiocytes, some with vacuolated cytoplasm and

TABLE 3

Other Clinical Features Encountered

	Number	
1. Patients who had proved diabetes insipidus or who subsequently developed this complication	6	
2. Osseous lesions of eosinophilic granuloma:	7	
(a) Proved by biopsy		5
(b) Roentgenographic demonstration only		2
3. Spontaneous pneumothorax:	9	
(a) Single episode		5
(b) Recurrent episodes		4
4. Peripheral blood eosinophilia (Greater than 6% of total WBC)	4	

some containing golden brown pigment having the appearance of hemosiderin. In certain areas there were small collections of lymphocytes. Multinucleated giant cells were occasionally seen. In some areas, relatively normal lung tissue could be seen adjacent to the histiocytic collections, while in other sections, many areas of histiocytosis were encountered. Well-defined fibrosis was not evident in our cases.

The pathology of pulmonary eosinophilic granuloma was reviewed by Auld in 1957.[26] His observations were based largely on his studies of the lung biopsies from five cases, and on a survey of the pertinent literature to that date. The author proposed the following sequence in the development of the pathologic picture: Briefly, a focal interstitial granuloma associated with a proliferative endarteritis was the earliest change. The alveolar structures were preserved but, with progression, the bronchioles, alveolar ducts and septa became involved by histiocytic proliferation. Bronchiolar destruction occurred and secondary emphysema developed. The obliterative arteriolitis led to tissue necrosis, with formation of communicating cavities. Expansion of these cavities could take place, and eventual pleural rupture

occur, accounting for the episodes of spontaneous pneumothorax. Auld further stressed that all stages of the disease process may be found in one small specimen of lung and noted that concomitant destruction and repair take place. He concluded that, as suggested on radiographs, permanent fibrosis does occur, and wondered whether certain instances of pulmonary fibrosis of undetermined etiology initiated originally with eosinophilic granuloma. Heppleston [10] has shown that this is true.

The majority of descriptions of the microscopic anatomy as seen in the biopsy specimens from other cases are in agreement with this. Nadeau and his associates [36] emphasize the fact that the essential histologic feature of this disease is histiocytosis involving the alveolar septa and bronchial walls. Arteriolitis, as stressed by Auld, may also be a significant feature.

We have attempted to correlate certain radiographic features with the described microscopic changes. The nodulations seen on roentgenograms are undoubtedly a reflection of the areas of intense inflammation and histiocytic proliferation. Since bronchiolar wall invasion and destruction are common, this and the resultant focal overdistention may well account for the radiolucencies or "cysts" seen in many of the radiographs. One end result of this process, as outlined by Auld [26] and stressed by the Mayo Clinic study,[36] is interstitial fibrosis and the formation of multiple parenchymal cysts, which may be lined by columnar epithelium or entirely by fibrous tissues. This process can produce the picture of the so-called "honeycomb lung." Heppleston,[10] in his detailed studies of the pathology of this phenomenon, points out that the "honeycomb lung" may result from a number of pulmonary diseases, including eosinophilic granuloma, sarcoidosis, berylliosis, treated tuberculous bronchopneumonia, scleroderma, and tuberous sclerosis. But to judge by the radiographic clearing in a number of cases of pulmonary eosinophilic granuloma, fibrosis and permanent change would not seem to be inevitable.

Pulmonary Function: Mazze and his associates [31] reported detailed pulmonary function studies on six patients, aged 19 to 42 years, with pulmonary eosinophilic granuloma seen at the St. Albans (New York) Naval Hospital. All showed elevation in the functional residual capacity, and the residual volume/total lung capacity ratio was above 30% in each case. There was no evidence of significant obstructive impairment on the spirogram, and the alveolar mixing (nitrogen washout method) was normal. Arterial blood oxygen saturations were normal at rest in three patients, and slightly decreased (88% saturation) in one. Lung compliance was reduced in four cases. None exhibited hypercapnia. One patient, who received no therapy, showed some worsening over a two-year period, with evidence of increasing hyperinflation. Another patient showed no real change in pulmonary function over an eight-year period, during which time there was clinical and radiographic improvement, although the chest roentgenogram did not com-

pletely clear. Mazzitello [20] noted an increase in the residual lung volume in one of his reported cases of pulmonary eosinophilic granuloma.

In case 5 of the present series, lung volume studies were done two years after the diagnosis of pulmonary eosinophilic granuloma had been made. The patient had received corticosteroid therapy (prednisone, 10 mg. daily) for a period of 13 months. During this time the chest film showed gradual clearing, and he became asymptomatic. Pulmonary function tests in March, 1960, showed a normal total vital capacity and maximal breathing capacity. The total lung volume was normal (5.5 L.), and the residual volume was 25% of the total lung capacity. The spirogram, however, showed some evidence of airway obstruction, the one-second vital capacity being only 43% of the total vital capacity, and the maximal midexpiratory flow rate reduced to 1.5 L. per second. The midexpiratory time was 1.3 seconds. The intra-

TABLE 4

Type of Therapy Given	Number of Patients	Average Length of Follow-Up (Months)	Patients Initially Asymptomatic	Patients with Symptomatic Improvement	Patients with No Follow-up Data	Change Seen on Chest Roentgenogram			
						No Change	Moderate Clearing	Marked Clearing	No Information
I. No therapy	13	34	1	9	2	3	3	3	4
II. ACTH and/or corticosteroids	20	13	3	11	4	5	10	3	2
III. X-radiation	5	17	—	2	2	1	2	1	*
IV. X-radiation and corticosteroids	4	10	2	—	1	2	1	—	1
V. Other therapy (antimicrobials)	3	18	1	2	—	2	1	—	(—)

* One roentgenogram showed "increased fibrosis" in a 32-month follow-up period.

pulmonary mixing (helium equilibration time) was normal. In the series reported from the Mayo Clinic,[36] two of the three patients studied showed arterial oxygen desaturation with exercise, and all three showed some diminution in the total vital capacity. One patient with advanced disease (who later died of cor pulmonale) demonstrated arterial oxygen desaturation at rest, increased functional residual capacity, and evidence of impaired intrapulmonary mixing.

Renzetti and his co-workers [12] reported the case of a 32-year-old man with diffuse pulmonary infiltrations, an osteolytic lesion in the skull, and diabetes insipidus. A diagnosis of disseminated histiocytosis was confirmed by autopsy. This patient had presented with the picture of the syndrome of "alveolar-capillary block," with marked defect of the diffusing capacity of the lung for oxygen and carbon monoxide. There was also a marked reduction in the total lung capacity. However, as in the other cases, the alveolar mixing index (nitrogen washout) and arterial pCO_2 were normal. This patient was treated with prednisone for 17 days, and repeat

testing revealed an improvement in the arterial oxygen saturation and also an increase in the total lung volume. There was no demonstrable change in the diffusing capacity, and the authors concluded that the improved oxygenation was due to a change in the ventilation-perfusion relationships.

Therapy and Follow-up: In Table 4 the 45 cases have been categorized as to type of therapy given (including no treatment), and a numerical breakdown has been made of the symptomatic and radiographic changes, if any. In such a small series of patients, it is obvious that statistical data are not valid, and certainly no conclusions should be drawn. However, since those who may encounter this disease will naturally be curious as to what types of therapy have been tried, we have merely outlined these data as gathered from the case reports. In many cases it was not possible to determine the exact length of therapy or the dosages used. Furthermore, the average lengths of the follow-up periods are influenced at one extreme by several patients who have been followed for from six to nine years (and who are asymptomatic, with roentgenographic clearing), and at the other extreme by a number of military patients who were returned to active duty or medically retired after a few months of observation following establishment of diagnosis.

The justification for x-ray therapy in pulmonary eosinophilic granuloma arises primarily from the well-known beneficial effect of this form of treatment in eosinophilic granuloma of the bone. Corticosteroid therapy was originally given because of the improvement observed in certain cases of acute or subacute disseminated histiocytosis X (Letterer-Siwe disease and Schüller-Christian disease). Several of the earlier cases of pulmonary eosinophilic granuloma showed improvement in both the patient's symptoms and the chest roentgenogram with no therapy at all. This observation no doubt led those treating later cases to use this approach, especially in the asymptomatic patient. Unquestionably, spontaneous remissions occur in this disease. Furthermore, the response to other therapies may well be influenced by the recency of the pulmonary lesions. This factor is most difficult to determine. Nadeau and his associates,[36] on the basis of their analysis of 28 cases of pulmonary eosinophilic granuloma, suggest a trial of corticosteroids in all patients in whom the diagnosis is made. Based on the data available at present, we believe that each case should be considered individually, and the choice of treatment guided by such factors as the severity of symptoms, the extent of pulmonary involvement, the recency of onset, and the facilities available for adequate follow-up.

Summary and Conclusions

Since 1951, 45 biopsy-proved cases of pulmonary eosinophilic granuloma (histiocytosis X) have been reported. From an analysis of the clinical and pathologic features, a general concept may be formulated.

1. This particular manifestation of histiocytosis X is seen most often in white males in the younger age group. The symptoms, if any, are usually mild, and cough is a common complaint. A variety of changes are seen on the chest film, but a diffuse, small nodular type of infiltration is the most common. Small cystic areas are also seen.

2. Biopsies of extrapulmonary sites are almost always unproductive. Lung biopsy is the only certain method for diagnosis. The pathologic picture is the same as that seen in eosinophilic granuloma of bone and supports the concept that pulmonary involvement is a manifestation of disseminated histiocytosis X. Sites of extrapulmonary change may be found in the bones and central nervous system. However, from clinical observations, patients presenting with pulmonary histiocytosis usually do not show evidence of involvement in other organ systems.

3. Pulmonary fibrosis and cystic changes of the lung may result from pulmonary eosinophilic granuloma, and death from cor pulmonale and respiratory failure may occur. However, as judged from the available follow-up information from 45 cases, the lesions tend to regress, and clinical improvement, rather than progression to pulmonary insufficiency, or at least stability, is most often seen; it is not possible to conclude whether any type of therapy (or none at all) hastens regression. Continued and more nearly complete follow-up data are, of course, needed.

4. Finally, pulmonary eosinophilic granuloma must be considered in the differential diagnosis of the patient with few or no symptoms and a chest roentgenogram showing diffuse nodular infiltrations. As diagnostic lung biopsy is more widely employed, it is anticipated that many more instances of this disease will be encountered.

Summario in Interlingua

Es recognoscite depost longo que "histiocytosis X"—le termino esseva formulate per Lichtenstein como designation inclusive pro le relationate conditiones de morbo de Schüller-Christian, morbo de Letterer-Siwe, e granuloma eosinophilic de osso—pote afficer multe systemas organic, incluse le pulmones. In 1951, le prime bioptica-mente documentate casos de primari affectiones pulmonar esseva reportate. Depost ille tempore, reportos ha apparite de un total de 45 casos de granuloma eosinophilic pulmonar in que le diagnose esseva provate per biopsias pulmonar. Iste total de 45 casos include le cinque del presente reporto.

Trenta-novem del 45 casos concerneva patientes mascule de un etate medie de 31 annos. Omnes, con un exception, esseva de racia blanc. In le majoritate del casos, pauc symptomas esseva symptomas pulmonar. Le gravamine le plus commun in iste categoria esseva un tusse sic. Septe patientes esseva completemente asympto-matic. Le constatation typic in le roentgenogramma thoracic esseva un diffuse infiltrato nodular, con un certe grado de confluentia in varie areas e exhibiente frequentemente multiple alterationes cystic. Altere studios laboratorial esseva non-revelatori. Eosinophilia de sanguine peripheric esseva rar. Complicationes non esseva absente: Pneumothorace spontanee esseva reportate in novem casos; lesiones ossee de granuloma eosinophilic esseva provate in cinque; e diabete insipide se dis-veloppava in sex.

Ab le puncto de vista pathologic, le lesiones pulmonar es characterisate per un proliferation histiocytic e eosinophilic in le septos alveolar e le parietes bronchiolar. Arteriolitis e destruction de parietes bronchiolar es describite. Le secunde de istos es probabilemente le base pro le alterationes cystic, le quales—quando illos es al superficie del pulmon—pote rupturar se con le resultato de pneumothorace.

Ab le puncto de vista clinic, histiocytosis pare esser un morbo benigne, characterisate per le tendentia de entrar in remission plus tosto que de progreder verso invaliditate pulmonar. Tamen, in casos sporadic tal invaliditate ha occurrite. Le syndrome de bloco alveolo-capillar esseva documentate in un caso. Varie formas de therapia—incluse corticosteroides, antibioticos, e radios X—ha essite usate, sed inadequate datos de observation posterior nunc disponibile e le basse numero del patientes studiate rende un evalutation therapeutic difficile. Le spontanee acclaration del lesiones pulmonar in le absentia de un tractamento specific non es incommun.

Le diagnose de granuloma eosinophilic pulmonar (o de histiocytosis X) pote esser facite con certitude solmente per biopsia pulmonar. Iste condition debe esser prendite in consideration in le diagnose differential de un relativemente asymptomatic patiente in qui le roentgenogramma thoracic monstra diffuse infiltrationes nodular.

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MEDICAL MEDIASTINAL EMPHYSEMA *

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INTRODUCTION

MEDIASTINAL emphysema is characterized by the presence of air in the mediastinum, and has been recognized at least since 1819, when Laennec described it under the title of "interlobular emphysema" as follows: "This affectation is characterized by infiltration of air between the lobules of the lung. . . . When the extravasation exists near the roots of the lungs, it speedily extends to the mediastinum, and from thence crosses to the neck and over the whole subcutaneous and intermuscular cellular substance of the body." [1] In 1939 Hamman [2] reported seven cases of spontaneous mediastinal emphysema—that is, mediastinal emphysema occurring in apparently healthy individuals, with no underlying disease demonstrable.

Mediastinal emphysema arising either spontaneously or due to some underlying disease is called "medical mediastinal emphysema." This term excludes all cases resulting from trauma or from surgical, diagnostic, or therapeutic procedures. A patient (case 15) with medical mediastinal emphysema was studied on the medical wards of the John Hopkins Hospital recently and is reported in this paper, along with all cases of this disorder seen at this hospital in a 23-year period. A review of the literature concerning the etiology, symptomatology, pathophysiology, and treatment of this condition is included.

All of the cases of mediastinal emphysema seen at the Johns Hopkins Hospital from January, 1926, to October, 1959, were investigated, and those due to trauma, surgery, or a diagnostic or therapeutic procedure (tracheotomy, esophageal dilatation, esophagoscopy, etc.) were discarded. Cases were used only if one or more of the following criteria were met: (1) The demonstration of air in the mediastinum on x-ray; (2) the presence of subcutaneous emphysema which could not be explained on any other basis, and (3) the presence of a crunching or bubbling sound synchronous with the heart beat (Hamman's sign).

There were 15 such patients, three of whom (cases 2, 3 and 4) were reported in Hamman's paper.[2] Table 1 indicates the pertinent diagnostic and laboratory studies in the 15 cases. Five histories are presented in detail below.

* Received for publication May 13, 1960.

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TABLE 1

Case No.	Age	Sex	Pain Occurrence and Location	Dyspnea	Cyanosis	Subcutaneous Emphysema Occurrence and Location	Hamman's Sign	Cardiac Dullness	Mediastinal Emphysema on X-ray	Temp.	WBC	Cause
1	20	F	None	0	0	Neck & anterior upper half of chest	0	Normal	None	98.6	N.R.	Spontaneous mediastinal emphysema
2	17	M	Severe substernal back pain aggravated by breathing & swallowing	0	0	Neck, axillae & anterior chest	+	Normal	Present	101.2	13,000	Spontaneous mediastinal emphysema
3	29	M	Severe posterior left chest pain aggravated by respiration	Severe	0	None	+	Absent	No med. emphysema but left pneumothorax	99.4	18,000	Spontaneous mediastinal emphysema
4	16	M	Severe left lower chest pain	0	0	Neck & both supraclavicular fossae	+	Absent	Present with left pneumothorax	97	28,000	Spontaneous mediastinal emphysema
5	26	M	Left jaw, neck & upper chest	0		Neck & chest	0	Normal	None	99.4	12,250	Mediastinal & lung abscess with cellulitis
6	41	M	Substernal	Marked		Neck & anterior chest	0	Absent	None	104	2,750	Miliary TB
7	1½	M	?	0	0	Behind left ear, neck, chest to costal margin, arms to wrist, axillae	0	Absent	Present	103.4	10,000	Pneumococcal pneumonia
8	25	M	Excruciating pain in sternum & both supraclavicular fossae	0	0	Above left sternoclavicular joint	+	Normal	Present	99	9,350	Spontaneous mediastinal emphysema
9	22	M	Knifelike substernal pain	Severe		Neck, arms, chest & back	0	Normal	Present with right & left pneumothorax	103	17,000	Asthmatic bronchitis
10	3½	M	None	Moderate	0	Anterior neck	+	Normal	Present	99.5	12,600	Asthmatic bronchitis
11	2	M	?	Severe	0	Neck, both axillae, right arm to wrist	0	Normal	Present	100.4	10,700	Bronchitis
12	45	M	Sharp pain in left lower chest posteriorly	Marked	0	None	0	Normal	Air in left sup. mediastinum & left pneumothorax	99.4	6,200	Spontaneous mediastinal emphysema
13	71	F	Slight occ. substernal pain radiating down left arm	0	0	Chest including breasts, neck, axillae, shoulders	+	Normal	Present	98.8	5,200	Senile emphysema
14	15	M	Severe precordial & left axillary	Mild	0	Neck bilaterally & left axilla	+	Absent	Present	101	7,700	Asthmatic bronchitis
15	20	M	Sharp anterior chest	Moderate	0	Neck, axillae, anterior chest, supraclavicular fossae, arms to elbow	+	Absent	Present with right pneumothorax	101	13,400	Asthmatic bronchitis

Case Reports

Case 5. This 26-year-old white male truck driver was admitted on March 21, 1938, 13 days after having a tooth extracted. He had spent the preceeding 10 days in bed with anorexia, malaise, and a temperature varying between 100° and 104° F. His neck was swollen, and pus had extruded from the extraction site for a week prior to admission. During this week he developed a cough productive of dark, putrid sputum, and began having chills. On examination his temperature was 99.4° F.; pulse, 88; respiration, 22. There was cyanosis of the head and neck, with a hot, tender, swollen area extending from the angle of the jaw to the sternal notch. The swelling increased with coughing, and crepitus was felt in some areas of the neck. Pus, air, and blood exuded from the extraction site in the left molar region, and the left cervical and supraclavicular lymph nodes were enlarged. In the left upper chest there were dullness to percussion, diminished tubular breath sounds, and occasional bubbling râles. The heart border was easily percussed. The remainder of the physical examination was normal. The hematocrit was 35, and the white cell count was 12,250. A chest x-ray showed a mass in the superior mediastinum extending into the left interlobar fissure, believed to be fluid. On March 22, 1938, an incision was made in the neck, releasing a large quantity of foul-smelling gas and bloody pus, which had filled a pocket extending beneath the sternum. Cultures of this material revealed pneumococci and staphylococci (*S. aureus*), with no anaerobic organisms. The patient died in coma on March 28, 1938. Autopsy revealed osteomyelitis of the left mandible and cellulitis of the neck, with mediastinal abscess perforating the thoracic wall and extending into the left upper lobe, and confluent lobular pneumonia and abscesses in both lungs. It is postulated that air dissected from the lung through the mediastinum and into the neck along the path of the infection.

Case 6. This 41-year-old Negro male steel worker was admitted on February 26, 1941, with shortness of breath of two weeks' duration. The patient stated that he had been in good health until then, when he developed chest pain with chills and fever. He had a cough productive of sputum, but no hemoptysis. His appetite had remained fair, but he had lost weight and was so weak that he remained bedfast. He became extremely dyspneic and lightheaded whenever he sat up. His temperature was 104° F., pulse, 104; respiration, 40. The patient appeared to be severely ill, and showed recent weight loss. Respirations were rapid, and cyanosis was present. There was transient ophthalmoplegia, and tuberculomas were observed in the fundi. The lungs were hyperresonant, especially over the sternum. Fine crepitant râles were heard at both bases anteriorly, in both axillae, and in the left lung posteriorly. The cardiac outline could not be found by percussion, and the sounds were barely audible. There was hepatosplenomegaly. The hemoglobin was 16.5 gm., and the white cell count was 2,750. A chest x-ray showed miliary lesions in both lung fields, and subcutaneous emphysema above the left clavicle and in the neck. No acid-fast bacilli were seen on a smear. On February 28, 1941, the patient's neck became greatly distended with air which extended into the anterior chest. Respirations ceased abruptly. No autopsy was performed. The clinical diagnosis was miliary tuberculosis with rupture of an emphysematous bleb.

Case 8. This 25-year-old white male was admitted on October 10, 1944, with the chief complaint of excruciating pain in the left supraclavicular fossa which radiated down to the middle of the sternum. In the summer of 1938, after sleeping near an open window, the patient had experienced a dull aching pain in the left supraclavicular fossa which radiated to the sternum and was intensified by inspiration. This episode lasted two weeks. In early 1942 he noted the gradual onset of similar pain, which persisted for two weeks. At that time he was told that an electrocardiogram showed evidence of a myocarditis, and consequently he remained bedfast for three months. On December 24, 1943, he was seized with pain in the left shoulder

which spread across his chest and to the back of his right shoulder. Although the chest pain disappeared several days later, on admission he was unable to breathe deeply without pain. The temperature was 99° F., and the pulse was 100. The patient had no dyspnea or cyanosis. The lungs were clear to percussion and auscultation, and the heart border was found by percussion. The remainder of the physical examination was normal. Hemoglobin was 16.2 gm. with a white cell count of 9,350. The patient was discharged three days later with the diagnosis of mediastinal emphysema. On January 20, 1944, he was re-admitted with a "peculiar sensation" in his chest. The preceding night he had felt a gaseous sensation in his epigastrium which was not relieved by alkali. He gagged himself to induce vomiting, which initiated a sensation like a "squirt gun loose inside my chest." This feeling spread into his neck, and he developed pain in both shoulders, accentuated by coughing and breathing. There was no change in the physical examination until the following day, when crepitation was felt above the left sternoclavicular joint. A to-and-fro friction rub was heard over the lower end of the sternum which varied with respiration. A chest x-ray demonstrated air in the mediastinum. These signs disappeared the next day, and he was discharged on January 24, 1944, with the diagnosis of spontaneous mediastinal emphysema.

Case 13. This 71-year-old white female was admitted on February 14, 1953, with the chief complaint of a "strange feeling" in her throat of five days' duration. Five days previously, while shopping, she had noticed a peculiar feeling in her throat, like a sore throat. That night she developed chills and fever, with diaphoresis but no cough. Two days later, on climbing the stairs, she noted the onset of exertional dyspnea and palpitation, without any other signs of cardiac difficulties. Her voice developed a nasal quality. That evening she had several episodes of slight substernal pain radiating down the left arm to the elbow. On the day prior to admission her neck became large and felt "crunchy." Her temperature was 98.8° F.; pulse, 138; respiration, 24. She had marked subcutaneous emphysema in her neck extending to the jaw, her shoulders, both axillae, and down her chest wall into her breasts. Her voice had a nasal quality, and she had no respiratory distress. Her lungs were hyperresonant, with normal fremitus and diminished breath sounds at both bases posteriorly. There were "loud crepitant sounds in the midportion of the chest and crepitant râles with systole and diastole." The heart border was found by percussion. The hematocrit was 46, and the white cell count was 5,200. A chest x-ray was reported as showing fibrotic infiltration of both lungs, with many emphysematous blebs on the right side. Although not reported at the time, mediastinal emphysema was present on the chest x-ray. The patient was given phenobarbital and digitoxin, and showed marked improvement in two days. However, on February 19 the subcutaneous emphysema was noted to increase and could be felt in her back, although she had no pain or dyspnea. Her temperature rose to 103° F., and penicillin was administered. Because she had not improved five days later, she was given 95% oxygen by mask for three hours, with dramatic improvement. The patient was discharged on March 3, 1953, with the diagnoses of senile emphysema and rupture of an emphysematous bleb with mediastinal emphysema.

Case 15. This 20-year-old Negro male was admitted on September 13, 1959, with the chief complaint of dyspnea and a swollen neck. The patient's mother had been at home for several months in the recent past with active tuberculosis. The patient described a feeling suggestive of subcutaneous emphysema in the right axilla, occurring intermittently since July, 1959. Nine days prior to admission he had wakened during the night with a severe paroxysm of coughing and breathlessness. Similar episodes occurred the next three nights, followed by sharp, diffuse pain in the anterior chest associated with the cough. Three days prior to admission he noted the onset of exertional dyspnea and wheezing, with swelling in the neck and

tightness in his chest when lying supine. He denied previous history of asthma, fever, chills or hemoptysis. The temperature was 101° F.; pulse, 90; respiration, 20. The patient was dyspneic but not cyanotic. There was crepitant swelling in the supraclavicular fossae, neck, anterior chest, axillae, and down both arms to the elbows. The lungs were normal to percussion, but diffuse wheezes were heard on auscultation. The cardiac outline could not be found by percussion, and the sounds

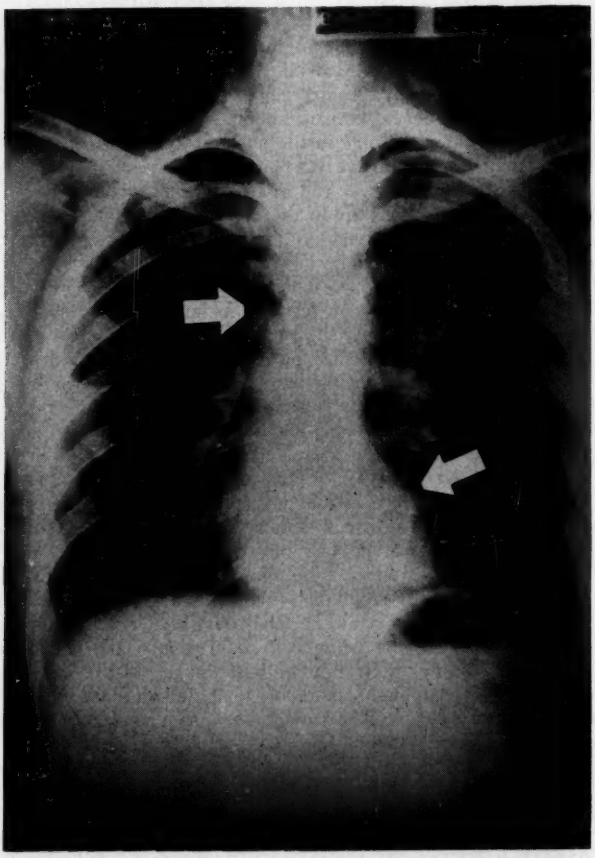

FIG. 1. *Case 15.* Chest x-ray taken on day of admission, showing mediastinal and subcutaneous emphysema. Arrows point to the pleural lining bordering the mediastinum. There is a small pneumothorax in the right apex.

were distant. There were prominent crunching and bubbling sounds with each systole, best heard with the patient lying supine. The physical examination was otherwise unremarkable. Hematocrit was 44, with a white cell count of 13,400. A chest x-ray showed mediastinal and subcutaneous emphysema, with a small right apical pneumothorax (Figure 1). Sputum culture revealed pneumococci, but there was no other evidence of pneumonia or tuberculosis. The patient was given chloramphenicol. The subcutaneous emphysema increased during the subsequent two days, then gradually disappeared. The patient was discharged on September 19,

1959, much improved, with the diagnosis of mediastinal emphysema secondary to asthmatic bronchitis.

Analysis of Cases

I. Incidence: During the period from January, 1926, to October, 1959, there were 634,612 in-patient admissions to The Johns Hopkins Hospital. Only 15 cases of medical mediastinal emphysema were seen, an incidence of about one in 40,000 admissions. It is possible that more cases were seen but remained unrecognized. Four cases diagnosed as mediastinal emphysema were discarded because they did not meet the criteria necessary for inclusion in this study.

II. Etiology: In this series, six cases, or 40%, were diagnosed as spontaneous mediastinal emphysema. In two of these six (cases 1 and 8) there was a history of vomiting associated with the development of this condition. Six of the patients had episodes of coughing, four associated with asthmatic bronchitis, one with pneumonia, and one with bronchiolitis. The remaining three patients had senile emphysema, terminal miliary tuberculosis, and cellulitis of the neck with mediastinal and lung abscesses secondary to tooth extraction.

III. Age and Sex: There were 13 males (87%) and two females (13%). Of the patients with spontaneous mediastinal emphysema, only one female was affected.

Mediastinal emphysema due to any cause was most common in the age group of 11 to 30 years (nine cases, or 60%). There were three patients in the group of 0 to 10 years, and three in the group over 30. In the cases of spontaneous mediastinal emphysema, one patient was 45 years old and the remaining five were 16 to 29 years old.

IV. Mortality: Although two of the patients in this series died (cases 5 and 6), mediastinal emphysema could not be implicated as the cause of death. However, it may have played a contributing role in one patient (case 6), who developed mediastinal emphysema as a complication of miliary tuberculosis. The other patient had mediastinal and lung abscesses, with mediastinal emphysema as a minor consequence.

V. Signs and Symptoms: Eight cases, or 53%, had dyspnea, which was usually moderate to severe. However, in six of these cases there was an underlying disease which contributed to the dyspnea. In only three cases was there any cyanosis, an incidence of 20%. Two of these patients were terminal. Twelve patients suffered pain (80%), and it was severe in eight. The severity of the pain was not related to the etiology of the mediastinal emphysema.

Subcutaneous emphysema was present in 13 cases (87%). The only cases in which it was not present were those of two patients with spontaneous mediastinal emphysema and spontaneous pneumothorax. Hamman's sign was present in only 53% of the cases. Diminution of cardiac dullness was mentioned in six cases (40%). Air in the mediastinum was observed

on x-ray in 11 patients (73%). In one patient with a pneumothorax obvious clinically, there were no signs of mediastinal emphysema except on chest x-ray, where air was seen "protruding in the region of the superior mediastinum." It is possible that air would have been found in the mediastinum in all x-rays if they had been carefully examined for it. In case 13 the x-ray report did not mention mediastinal emphysema, yet it is present on review of the x-rays.

Five patients had a pneumothorax, one being on the right side (case 15), which is unusual. The presence of a temperature elevation usually depended on underlying disease, but one patient (case 2) had a temperature of 101.2° F. with spontaneous mediastinal emphysema. Leukocyte counts varied from 2,750 to 28,000, the highest occurring in a patient with spontaneous mediastinal emphysema, and the lowest in the patient who succumbed to miliary tuberculosis.

Discussion

Laennec [1] described the following conditions as etiologic factors in mediastinal emphysema: "The most common of these is the prolonged forcible retention of the breath during powerful and long-continued exertions, as in child-bed, in relieving the bowels when constipated, and particularly in raising heavy weights. Children are more subject to this disease than adults. In them it occurs frequently during an attack of croup, or in severe catarrh in which the bronchial obstruction is very great."

Draper [3] found 42 cases of spontaneous mediastinal emphysema in his review. Of these, 62% occurred in the 20- to 29-year-old range. Dickie [4] found 14 cases in 18,000 university students. Five cases of mediastinal emphysema were reported by Phillips [5] in 6,650 deliveries, all in young primiparas (18 to 21 years old) who had an otherwise normal labor and delivery. Clark and Synnott [6] found 20 cases in influenza pneumonia, with only three recoveries. Twenty-five cases associated with bronchial asthma were reported by Schwartz.[7] A case of mediastinal and subcutaneous emphysema due to rupture of an emphysematous bleb occurred in a patient with smallpox, as reported by Wilkinson.[8] Burton and Weir [9] found seven cases of subcutaneous emphysema in diphtheria which they believed were due to perforation of the trachea or rupture of alveoli. Worden and Chaisson [10] noted a case following pertussis. Welty[11] observed a case associated with perforation of a peptic ulcer. Macklin and Macklin [12] mentioned cases associated with measles and pneumonia, and one following a pulmonary embolism. Several cases have occurred in the same family, suggesting a hereditary weakness of the lung.

Although usually a benign disease, mediastinal emphysema may cause death. Macklin and Macklin [12] list the following situations as dangerous:

1. When the presence of air bubbles around blood vessels and the heart interferes with circulation.

2. When massed air bubbles in pulmonic interstitial tissue cause splinting of the lung in inspiratory position, making respiration difficult.
3. When pressure in the mediastinum gets too high.
4. When an escape route to the neck does not open.
5. When air escapes into both pleural cavities, causing bilateral pneumothorax.
6. When there is serious inflammatory disease of the lungs.
7. When coughing causes a tension pneumothorax.
8. When the condition occurs with atelectasis of the newborn.

Those signs and symptoms associated with this disorder are dyspnea, pain, subcutaneous emphysema, diminution of cardiac dullness, Hamman's sign, cyanosis, and air in the mediastinum on chest x-ray (Table 1). It is interesting to note that Laennec[1] was aware of the so-called Hamman's sign, about which he wrote: "There is one sign completely pathognomonic of the affection, viz., the dry crepitus rattle with large bubbles. . . . Together with this sign we usually perceive also, during inspiration and expiration, a sound or sensation as of one or more bodies rising and falling and rubbing against the ribs." Hamman's sign will be present only if air is located between the heart and the anterior chest wall. In Macklin's[13] experiments, air was never demonstrated in the pericardium.

Macklin[14] has shown that mediastinal emphysema results from fine bubbles of air which rupture through the alveoli and dissect along the sheaths of blood vessels, coalescing to form large bubbles in the mediastinum. He has postulated that the only alveoli which rupture are marginal ones—those whose bases abut on some structure other than alveoli or air passages. Tension develops in the connective tissue extending between the blood vessels and surrounding alveoli, causing rupture. Factors creating this tension are:

1. Overexpansion of alveoli, if the heart cannot pump sufficient blood into the pulmonary arteries to keep pace and expand the vessel lumen to the same degree.
2. Narrowing of the vessel lumen without decreasing alveolar expansion.
3. Development of pressure inside the alveolus greater than atmospheric pressure.

Rupture never occurs adjacent to a bronchiole, because the pressure there is the same as in the alveolus. The alveoli will not rupture if the chest is splinted, even if the pressure is quite high. Autopsy specimens have shown the blood vessels to be separated from the lung parenchyma by air, which distends the connective tissue and may compress the blood vessels. The most striking accumulation of air is at the roots, where it impinges on main vessels. Air has never been found in the sheaths of bronchioles. Anginal pain may be created by air compressing the coronary arteries.

Although the air may form blebs beneath the visceral pleura, pneumo-

thorax in these cases is caused only by rupture of the mediastinal wall. Mediastinal emphysema is never caused by pneumothorax.

Ballon and Francis[15] have shown that dyspnea and cyanosis in mediastinal emphysema are usually due to compression of blood vessels and not of bronchi. If mediastinal pressure is increased the blood pressure will decrease, and this is most pronounced if this pressure increase is in the anterior mediastinum. They found that if mediastinal emphysema is marked, subcutaneous emphysema is slight, and vice versa. Torrey and Grosh[16] described this clinically: ". . . When in apparent respiratory extremis, frequently a patient would begin to complain of pains, substernal and in the jugular fossae, and crepitation would be noted in the subcutaneous tissues at the root of the neck, and immediate marked subjective relief was apparent, rapidly followed by a noticeable improvement in the respiratory excursion of the chest, and the most striking decrease in cyanosis and jugular distention. . . ."

Laennec[1] recommended the following treatment: "When the aerial infiltration extends to the external parts, a few pricks with the lancet at the lower part of the neck or wherever the emphysema is greatest, usually suffice to dissipate it. When it is confined to the lungs, the air appears to be always absorbed, and the interlobular partitions gradually return to their natural state. I never met a fatal result from this disease alone. . . ."

In 1884 Bisshopp[17] reported a case of a four-year-old boy who was run over by a dung-cart and developed pronounced subcutaneous emphysema. The patient was in extremis and was treated in the following manner. "He was put in a tent in front of the fire, and a steam kettle was kept going. Nine or ten punctures were made in the neck, back, cheek, and dorsal region . . . and when the air rushed out, it hissed, and blew out the flame of a wax-light. The operation at once greatly relieved the patient," who eventually recovered. Another method, recommended by Albernathy in 1816,[18] was bandaging the area tightly.

More recently Fine et al.[19, 20] have shown that subcutaneous emphysema and mediastinal emphysema can be relieved by breathing 95% oxygen. The theory behind this therapy is that the oxygen in the tissue air is rapidly absorbed, leaving nitrogen in the tissues. The rate of diffusion of a gas across a semipermeable membrane is proportional to the difference in partial pressure of the gas on the two sides. Nitrogen diffuses slowly from the tissues into the blood because its partial pressure in tissue is 627 mm. Hg, and in blood is 573 mm. Hg. After one hour of breathing 95% oxygen the partial pressure of nitrogen in the blood falls to 155 mm. Hg, and by four hours it falls to 31 mm. Hg.

Although five patients in this series received oxygen, only one (case 13) received 95% oxygen by mask. After three hours of this treatment there was dramatic relief of her signs and symptoms.

In the last two years Schulte[21] and Norman and Rizzolo[22] have reported cases of mediastinal and subcutaneous emphysema during submarine train-

ing after subjects have been placed in a pressure chamber. They have removed the emphysema by placing the patient in a compression chamber again and increasing the pressure to six atmospheres absolute, at which time all emphysema disappears. The pressure is allowed to return slowly to normal after many hours. The theory behind this treatment is that at six atmospheres of pressure the air bubbles are reduced to one-sixth their size, which allows a more rapid reabsorption. Obviously this form of therapy is not available for general use, nor does it seem to offer any advantages over 95% oxygen inhalation.

Conclusions and Summary

Medical mediastinal emphysema is a rare disease. The most common cause in this series is spontaneous mediastinal emphysema. It affects males predominantly, and occurs most frequently in the age group of 11 to 30 years. It is almost always a benign disease, but has the potentiality of becoming serious. The most common signs and symptoms are dyspnea, chest or back pain, subcutaneous emphysema, Hamman's sign, and air in the mediastinum on x-ray. Air enters the mediastinum from ruptured alveoli and travels along the blood vessel sheaths. Treatment is rarely necessary, but the simplest and most efficacious method is breathing 95% oxygen by mask.

Acknowledgments

The author is indebted to Dr. Frank L. Iber and Dr. Gottlieb C. Friesinger for their assistance in the preparation of this paper.

Summario in Interlingua

Le termino "emphysema mediastinal medical" coperi omne le casos de emphysema mediastinal que se declara spontaneemente o que resulta de un subjacente processo pathologic. Dece-cinque tal casos es reportate, representante le complete casuistica del Hospital Johns Hopkins in le curso de un periodo de 23 annos. Le incidentia es assi circa un in 40.000 hospitalisationes. Sex del casos esseva diagnosticate como emphysema mediastinal spontanee. Inter le remanente novem, quatro habeva bronchitis asthmatic e le altere cinque pneumonia, emphysema senil, bronchiolitis, tuberculosis miliari terminal, e cellulitis del collo con abscessos mediastinal e pulmonar secundari al extraction de un dente. Le morbo affice predominantemente subjectos de sexo mascule e occurre le plus frequentemente in le gruppo de inter 11 e 30 annos de etate. Le signos e symptomas es dyspnea, dolores thoracic o dorsal, emphysema subcutanee, signo de Hamman (i.e. le presentia de un sono craccante o bulliente in synchronia con le pulso cardiac), evidentia radioscopic de aere in le mediastino, diminution del matitate cardiac, e—occasionalmente—cyanosis. Un tertio del patientes habeva un associate pneumothorace. Isto occurreva in un caso al latere dextere, lo que es inusual. Il ha essite demonstrate que emphysema mediastinal resulta ab micre bullas de aere que erumpe ab le alveolos e progrede al longo del vainas del vasos de sanguine, coalescente in grande bullas in le mediastino. Ben que le aere pote confluer in discrete massas vesiculiforme infra le pleuro visceral, pneumothorace occurre in iste casos exclusivemente in consequentia de un ruptura del pariete mediastinal. Emphysema mediastinal es nunquam causate per pneumothorace. Dyspnea e cyanosis es usualmente le effecto de compression del vasos de sanguine e non de

compression de bronchos. Dolores anginal pote esser causate per le pression del aere contra le arterias coronari. Si le emphysema mediastinal es marcate, le emphysema subcutanee es leve e vice versa. Le plus frequentemente le morbo es benigne, sed illo ha le potentialitate de devenir grave. Tractamento es necessari rarmente, e le plus simple e le plus efficace methodo es le respiration de 95% de oxygeno per un masca.

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COMMON CHARACTERISTICS OF LEPTOSPIROSIS: A REPORT ON 11 CASES *

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THE human leptospiral infections have been grouped into various clinical syndromes, such as a mild, grippelike illness, an aseptic meningitis, and a sometimes fatal complex of jaundice, nephritis, hemorrhage, and vascular collapse known as Weil's disease. A recent outbreak of leptospirosis on Okinawa among 11 U. S. Marines supports the observation of Asian, European, and American clinicians that leptospirosis most commonly presents as a mild illness, with only slight renal and hepatic damage, plus delayed signs of aseptic meningitis.

TABLE 1

Incidence of Clinical Manifestations in 11 Cases of Leptospirosis

Manifestations	Cases (No.)
Fever	11
Chills	11
Headache	11
Anorexia	11
Myalgia	10
Conjunctivitis	7
Retro-orbital Pain	7
Nausea and Vomiting	6
Diarrhea	6
Herpes Simplex Labialis	5
Nuchal Rigidity	5
Abdominal Pain	4
Meningitis	3
Pneumonitis	1
Splenomegaly	0
Hepatomegaly	0
Jaundice	0

Edwards,[1] in his recent study of 12 sporadic cases of leptospiral disease, has pointed out that this rather distinct, mild, and common form of leptospirosis can follow infection with *any* of the numerous leptospiral serotypes.

The 11 Marines whose cases will be discussed in this report had all swum in a natural, stagnant-appearing pond nine to 14 days before the onset of symptoms. The initial clinical manifestations distinguishing the group included chills, fever, headache, lumbar and calf pain, anorexia, and conjunctivitis (Table 1). To the admitting officer, these findings suggested a formidable list of infectious diseases from which to choose his diagnosis. Leptospirosis was moved to the top of this list following the rather con-

* Received for publication May 25, 1960.

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TABLE 2

Laboratory Data in 11 Cases of Leptospirosis

Test Results	Cases (No.)
Leukocytosis	9
Elevated SGOT Values (over 40 units)	9
Abnormal Urinary Sediment (Increased No. WBC, RBC and/or casts)	8
Albuminuria	8
Pleocytosis (CSF cell count over 10)	3
Elevated Serum Bilirubin	1

sistent finding in these 11 patients of leukocytosis, elevated serum glutamic-oxalacetic transaminase values, and abnormal urinary sediment (Table 2). The demonstration of pleocytosis in the spinal fluid of three of the patients lent further support to the final diagnosis. Eventually, serologic confirmation of leptospiral disease in this group was obtained (Table 3).

We report below the case of one of the patients who embodied virtually all of the clinical manifestations seen in the group as a whole.

CASE REPORT

Case 1. A 21-year-old white male Marine was admitted to the contagious disease ward of the U. S. Army Hospital, Ryukyu Islands, on August 6, 1959. Twelve

TABLE 3

Agglutination Studies: Leptospiral Titers

Case	Day of Illness on Which Serum Was Taken	*L. autumnalis A*	*L. hebdomadis*	*L. semarang*	*L. australis ballico*
1	5	1:50	0	0	—
	26	1:400	1:400	1:400	—
2	6	1:50	1:50	1:200	—
	27	1:400	1:400	1:400	—
3	7	1:400	1:400	1:400	—
	28	1:400	1:200	1:200	—
4	7	1:50	1:100	1:400	—
	28	1:400	1:400	1:400	—
5	6	0	0	1:200	—
	27	1:800	1:400	1:1,600	—
6	8	—	1:100	1:400	1:50
	29	—	1:50	1:400	0
7	5	0	0	0	—
	26	1:400	1:400	1:200	—
8	3	0	0	0	—
	24	1:400	1:400	1:400	—
9	4	0	0	0	—
	17	1:200	1:100	1:200	—
10	6	1:100	0	0	—
	27	1:400	1:400	1:400	—

days prior to admission he had swum in a stagnant pond (during a lull in field maneuvers). Nine days later (three days before admission) he had an onset of lethargy, chills, fever, retro-orbital pain, and a steady frontal headache. He subsequently developed severe lumbar back pain, marked aching in his thighs and calves, vague upper abdominal pain, and a burning sensation in his eyes. In addition, he experienced anorexia, nausea, occasional vomiting, and mild diarrhea. He also began to cough frequently, the sputum being blood-streaked on several occasions.

There was no history of jaundice, dark urine, petechiae or ecchymoses, or symptoms of genitourinary tract infection.

On admission, the temperature was 102° F.; pulse, 84; respiration, 20; blood pressure, 115/70 mm. Hg.

The patient appeared to be slightly lethargic. He had no nuchal stiffness, but he complained of posterior neck tenderness on passive flexion. The conjunctivae were markedly injected. His throat was red. Lungs were clear to auscultation and percussion. There were no cardiovascular abnormalities. The liver and spleen were not palpable; there was moderate tenderness over the area of hepatic dullness. There was mild, generalized abdominal tenderness without guarding. Bowel sounds were normally active. Cranial nerves, as well as the motor and sensory systems, were completely intact. There was no rash or lymphadenopathy.

On admission, hemoglobin was 13 gm.%; hematocrit, 38%; corrected erythrocyte sedimentation rate, 33 mm./hr. White blood cell count was 14,700; neutrophils, 94% (including 11% band forms); lymphocytes, 6%. Admission urinalysis revealed a trace of albumin. Albuminuria was not present on the seventh hospital day. The sediment of centrifuged urine, on admission, showed 0 to 1 red blood cell and 4 to 5 white blood cells per high power field; on the seventeenth hospital day there were 8 to 10 white blood cells per high power field; on the following day, 1 to 3 white blood cells per high power field.

On the eleventh day of illness the platelet count, bleeding time, coagulation time, and prothrombin time were within normal limits. The cardiolipin microflocculation test of serum and spinal fluid showed no reaction.

Cerebrospinal fluid cell count on the eighth day of illness was 786 white blood cells per cubic millimeter; 54% were polymorphonuclears and 46% were lymphocytes. Cerebrospinal fluid sugar was 50 mg.%; chlorides, 120 mEq./L.; total protein, 62 mg.%. Twenty-two days after the onset of illness, cerebrospinal fluid cell count was 7 white blood cells per cubic millimeter (2 polymorphonuclears, 5 lymphocytes); cerebrospinal fluid sugar and protein values were within normal limits. Culture of both cerebrospinal fluid specimens showed no growth.

Serum glutamic-oxalacetic (SGO) transaminase value on the fifth day of illness was 150 units; on the eighth day, 238 units; on the fifteenth day, 8 units. Alkaline phosphatase on the ninth day of illness was 14.3 Bodansky units; total bilirubin, 1.0 mg.%; "direct" bilirubin, 0.5 mg.%; cephalin flocculation and thymol turbidity values, within normal limits. Examination for urine bile and urobilinogen was negative. On the eighteenth day of illness, bromsulfalein retention after 45 minutes was 0%.

On the fifth and twenty-sixth days after the onset of illness, a serum specimen was drawn for agglutination studies. The acute and convalescent serum specimens were tested against various serotypes, with the following titers:

	L. autumnalis A	*L. hebdomadis*	*L. semarang*
Acute phase serum	1:50	0	0
Convalescent phase serum	1:400	1:400	1:400

The fourfold or more rise in titer seen with each of these serotypes was interpreted as being confirmatory of leptospiral disease in this patient. The causative

organism in this case could not be inferred from the results because of cross-reactions commonly seen in the agglutination tests of leptospirosis. In fact, there is a probability that his serum was not tested against the specific serotype causing his disease.

In summary, this patient's significant laboratory findings were leukocytosis, albuminuria, abnormal urinary sediment, altered liver function, pleocytosis, and a diagnostic rise in titer against three leptospiral serotypes.

Hospital Course: The patient remained febrile for the first four hospital days, with daily temperature elevations between 100° and 104° F. The fever diminished by lysis on the eighth day of illness; no subsequent rise in temperature occurred.

A chest x-ray on admission revealed patchy densities in both upper lung fields, which were felt to represent an acute pneumonitis. The patient's slightly productive, frequent cough disappeared by the ninth day of illness; physical examination of his chest was repeatedly negative. On the eleventh day of illness a chest x-ray showed complete resolution of the previously noted infiltrates.

On the eighth day of illness the patient developed nuchal rigidity in the presence of his constant frontal headache. A spinal fluid specimen that day showed a marked pleocytosis. By the following day his headache had disappeared.

Several days after the onset of symptoms the patient developed an eruption of herpes simplex about his mouth. The lesions persisted for about one week.

On the thirteenth day of illness a liver biopsy was performed with a Vim-Silverman needle. The specimen consisted of histologically normal liver tissue.

On the fifth day of illness (second hospital day), the patient began receiving tetracycline, 500 mg. by mouth every six hours, following an initial dose of 1 gm. It was felt that the general clinical improvement which occurred on the seventh day of illness (two days after antibiotic therapy was begun) represented a stage in the natural course of this benign form of leptospirosis, rather than a salutary response to antibiotic therapy.

Throughout the first seven days of illness the patient's anorexia, nausea, myalgia, and conjunctivitis gradually subsided. A gradually decreasing malaise was present during the second week of illness. He was discharged from the hospital 19 days after the onset of symptoms, the spinal fluid cell count and liver function tests having returned to normal values.

Comment: This patient's clinical course was typical of the relatively mild disease which can follow infection with any of the leptospiral serotypes. The presence in this patient of conjunctivitis, lumbar and calf pain, headache, neck stiffness, abnormal liver function tests, microscopic pyuria, and pleocytosis established the clinical diagnosis beyond reasonable doubt. His having swum in a stagnant pond 12 days prior to the onset of his symptoms was an additional clue to the diagnosis.

The finding of a patchy pneumonitis in this case was consistent with leptospiral disease.[2] Signs of pneumonitis did not develop in the other 10 patients.

Discussion

Leptospirosis has been described as a biphasic illness, the first five to seven days of which have been termed the "septicemic" stage.[1] In this period of time, leptospirae can frequently be recovered from the blood and spinal fluid. The second stage begins after clinical improvement has occurred, on the sixth or seventh day. Shortly after the end of the first stage

there is commonly a secondary, brief, slight rise in temperature. The latter occurs following an afebrile period of from 12 to 24 hours.

Concomitant with the secondary rise in temperature there is the frequent development of meningitis, often heralded clinically by the sudden recurrence of headache, or by an intensification of a persistent headache. The blood and cerebrospinal fluid during this second stage of illness are sterile. Circulating antibodies begin to appear in this second stage, and rapidly rise in titer. Edwards concurs with Gsell's view [3] that the second stage manifestations of a secondary rise in temperature and the onset of meningitis, after about five to seven days of illness, are due to a hypersensitivity phenomenon. Edwards terms this period of the illness the "immune" stage. Before the seventh day of illness one cannot expect to find pleocytosis, even in the presence of headache and nuchal stiffness.[1]

Pleocytosis was demonstrated in three of the patients in the present study (Table 4).

During hospitalization, five of the 11 patients developed nuchal stiffness; these five were the only ones on whom a spinal puncture had been performed during the early period of hospitalization. The patient presented in detail above (case 1) was the only one of the five whose spinal fluid initially showed pleocytosis. The lumbar puncture on this patient was performed on the eighth day of illness; the spinal taps on the four other patients with nuchal stiffness were done on the first to sixth day of their illness.

On August 26 the 11 patients, all of whom had been discharged, were brought back to the hospital for spinal punctures. On this late date the cerebrospinal fluid of one of the four patients (case 3) with initially normal cerebrospinal fluid cell counts showed a pleocytosis of 20 white blood cells per cubic millimeter.

Consistent with the biphasic concept of leptospirosis, three of the 11 patients (cases 2, 4 and 6) showed an afebrile period of 12 to 36 hours on the fifth to seventh day of illness, with subsequent low-grade fever for from 12 to 24 hours. In one of these patients (case 2) a pleocytosis of 20 cells was demonstrated on August 26, 26 days after the onset of symptoms. This patient, during his hospitalization, had had a moderate headache but no nuchal stiffness. He had not had a spinal puncture prior to August 26.

The experience with these 11 patients bears out the observation of Edwards that (1) stiffness of the neck in the first phase of illness does not indicate meningitis, and (2) a pleocytosis in the second phase of illness can be found in either the presence or the absence of signs of clinical meningitis. According to Edwards and Gsell, if a spinal puncture is performed shortly after the seventh day of illness, a great majority of patients with leptospirosis will be found to have a pleocytosis.

The clinical course of all 11 patients was similar (Table 1). Shaking chills, high remittent fever, nonthrobbing frontal headache, retro-orbital pain, moderate anorexia, frequent nausea and vomiting, mild diarrhea,

myalgia of the lumbar area and of the lower extremities, and conjunctivitis were the most common clinical manifestations in the group during the first week of illness. Five patients developed lesions of herpes simplex about their mouths during the first few days of hospitalization.

Nine patients showed elevated SGO transaminase values. No patient exhibited clinical jaundice; only one (case 7) had an elevated total serum bilirubin (3.4 mg.%). Enlargement of the liver or spleen did not occur in the group. On two patients (cases 1 and 9) a liver biopsy was performed, one on the thirteenth day of illness, the other on the eighth day. Both patients had one or more abnormal liver function tests during the first two weeks of illness. Both biopsy specimens consisted of normal liver. The results of liver biopsy on two patients manifesting leptospirosis with jaundice were reported in 1951 and 1952. Each patient showed mild hepatocellular damage consistent with a mild hepatitis.[4]

No patient experienced azotemia; eight showed the presence of albuminuria; eight had red blood cells and increased numbers of white cells and/or casts in their urinary sediment on one or more specimens. Leukocytosis and elevated SGOT values were found in nine patients.

Dark field examination of blood specimens from several patients failed to reveal the presence of leptospirae. (The latter examination often proves to be unreliable because the appearance of leptospirae is similar to that of strands of fibrin being whipped about by brownian motion.) The lack of special culture media [5] and laboratory animals prevented attempts to isolate leptospirae from the blood or urine of the 11 patients.

No patient experienced the type of abdominal pain occasionally seen in leptospirosis which suggests acute appendicitis or cholecystitis, and can sometimes lead to surgical exploration.[6] Such rare manifestations of leptospirosis as iridocyclitis, peripheral neuritis, myelitis, alopecia, and leptospiral endocarditis were likewise not seen in this group of patients.

Ten of the patients received tetracycline; one, chloramphenicol. The dosage for both drugs was 1 gm. initially, followed by 0.5 gm. every six hours. Tetracycline was begun on the fourth to eighth day of illness in the 10 patients; the one patient on chloramphenicol began receiving this drug 24 hours after the onset of symptoms. The clinical progress of all 11 patients resembled the usually benign natural course of untreated leptospirosis. Antibiotic therapy in almost all patients was begun relatively late, in the "septicemic phase" of illness. It was felt that chemotherapy in these patients had little if any effect on their disease. The efficacy of antibiotic therapy in leptospirosis remains controversial,[7-9] but some observers believe that very large doses of penicillin or of a broad-spectrum antibiotic, given early in the disease, are probably of benefit.[10-12]

Acute- and convalescent-phase serum specimens on 10 of the 11 patients were submitted to the 406 Medical General Laboratory in Japan for agglutination studies. Unfortunately, paired sera were not obtained on the

eleventh patient. The serotypes used in testing were those of *Leptospira autumnalis A, Leptospira hebdomadis, Leptospira semarang,* and *Leptospira australis ballico.*

Serologic confirmation of leptospirosis on the basis of agglutination studies is considered to be established when (1) a fourfold or greater rise in antibody titer occurs during the course of illness, or (2) a titer of 1:400 or greater is sustained if the first serum specimen was obtained on or after the seventh day of illness.[1] All of the 10 patients studied met one or the

TABLE 4

Cerebrospinal Fluid Examination

Case	Day of Illness	White Blood Cells/cu. mm.	PMN'S (%)	Lymphocytes (%)	Protein (mg. %)	Sugar (mg. %)
1	8 25	786 7	54 30	46 70	62 44	50 70
2	27	20	0	100	52	70
3	1 28	3 20	0 0	100 100	37 32	68 75
4	6 26	3 9	0 10	100 90	28 38	90 60
5	5 25	2 5	0 0	100 100	26 35	100 75
6	27	4	0	100	21	70
7	24	0	0	0	40	70
8	7 23	2 7	0 0	100 100	24 27	56 60
9	18	8	0	100	51	85
10	25	3	0	100	30	90
11	23	8	0	100	36	65

other of these criteria. Diagnostic but comparatively low titers were found with *L. autumnalis A, L. hebdomadis A,* and *L. semarang* (Table 4). The remaining patient, whose serum was not studied, was felt to have had leptospirosis clinically.

As illustrated in the present study, agglutination results often do not point to the specific infecting serotype because of the phenomenon of cross-reaction among the numerous leptospiral serotypes. Nevertheless, agglutination results in these patients can be said to be confirmatory of leptospiral disease. As has been pointed out, the mild form of illness seen in the patients comprising this study can follow infection with any of the leptospiral species.

SUMMARIO IN INTERLINGUA

Un eruption recente de leptospirosis in 11 statounitese soldatos marin in Okinawa supporta le observation de clinicos asian, europee, e american que leptospirosis se presenta communmente como un leve maladia con moderate lesiones renal e hepatic, sequite per tardive signos de meningitis aseptic. Iste distincte, pauco grave, e commun forma de leptospirosis pote sequer le infection per non importa le qual del numerose serotypos leptospiral.

Le 11 soldatos marin habeva omnes natate in un stagno natural inter novem e 14 dies ante le declaration del symptomas. Le manifestationes includeva algor, febre, mal de capite, dolores lumbar e muscular in le suras, anorexia, e conjunctivitis. Cinque del patientes disveloppava rigiditate nuchal. Nausea e vomito occurreva in sex patientes, diarrhea in sex, e herpete simple labial in cinque. Nulle del patientes disveloppava jalnessa, hepatomegalia, o splenomegalia.

Elevate valores de transaminase glutamic-oxaloacetic del sero—indicante le presentia de inflammation hepatic—esseva trovate in novem patientes; leucocytosis occurreva in novem; cylindruria, pyuria, e/o hematuria microscopic in octo; e albuminuria in octo.

In tres patientes, specimens de liquido cerebrospinal prendite post le septime die del maladia monstrava pleocytosis (con numerationes de inter 20 e 786), sed culturas ab ille specimens esseva sterile.

Specimens seral ab 10 patientes in le phases acute e convalescente esseva studiate pro agglutininas contra varie serotypos leptospiral. In omne le apparente specimens, titros comparativemente basse sed diagnostic esseva trovate pro *Leptospira autumnalis A, Lept. hebdomadis A,* e *Lept. semarang.* Le specificamente causative organismos in iste casos non poteva esser deducite ab le resultatos a causa del reactiones cruciate que es communmente incontrate in le tests de agglutination pro leptospirosis.

On ha describite leptospirosis como un morbo biphasic. Durante le prime cinque a septe dies (i.e., le stadio "septicemic"), leptospiras pote frequentemente esser retrovate ab le sanguine e le fluido spinal. Post que un melioration clinic ha occurrite le sexte o le septime die, le secunde phase comencia con un leve e breve augmento secundari del temperatura, sequente un periodo de inter 12 e 24 horas de afebrilitate.

In concomitantia con iste augmento del temperatura, un frequente occurrentia es le disveloppamento de meningitis. Ante le septime die del morbo, il non es a expectar que pleocytosis es trovate, mesmo in le presentia de mal de capite e rigiditate nuchal. Durante le secunde stadio del morbo, le sanguine e le liquido cerebrospinal es sterile. Anticorpore comencia apparer in le circulation, con titros que monta rapidemente. Es opinate que iste manifestationes reflecte un phenomeno de hypersensibilitate. Iste phase del morbo ha essite designate como le stadio "immun."

Le observationes del curso clinic in le 11 patientes del presente reporto esseva congruente con le conception del biphasismo de leptospirosis.

Omne le patientes esseva tractate durante le stadio "septicemic" con antibioticos a large spectros. Le conclusion pareva justificate que iste agentes exerceva nulle effecto super le curso del morbo. Le complete restablimento de omne le patientes reflectava le plus probabilemente le benignitate natural del curso de iste forma de leptospirosis.

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RELATIONSHIP OF THE GRIESS NITRITE TEST TO BACTERIAL CULTURE IN THE DIAGNOSIS OF URINARY TRACT INFECTION *

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Interest has been renewed periodically in the Griess nitrite reaction as a means of detecting bacterial infection in urine.[1-4] Although it was originally employed as a test of bacterial contamination of water,[5] its application as an indicator of bacteriuria was suggested by the finding that most of the bacterial species which cause urinary tract infection reduce nitrate to nitrite.

In vitro studies by Kahler and Guze [6] have revealed that sodium nitrite in concentrations of as little as 0.1 μg. per milliliter gives a positive test. However, considerable periods of time were required for nitrate reduction by certain strains of bacteria. For example, it was necessary to incubate some cultures of *Escherichia coli, Aerobacter aerogenes, Pseudomonas* and *Paracolon* species for several hours before the test became positive. Nevertheless, because there is a need for a convenient method of mass detection of urinary tract infection, we have made a study of the test under conditions of potential use.

The present studies have been primarily concerned with the correlation between the Griess reaction and results of culture of urine for bacteria. They reveal, in general, that when the Griess test is positive, there is almost invariably a positive urine culture, but among patients with positive urine cultures only about 50% exhibit a positive Griess reaction. Details of the study are presented in the following report.

Material and Methods

Sources of Urine Specimens: * Two hundred ninety-three of 3,504 specimens of urine sent for routine urinalysis gave a positive Griess reaction. From 234 different patient-donors of these specimens, a second specimen

* Received for publication April 25, 1960.

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* All examinations of urine except the Griess tests were performed by the Clinical Pathology staff of the Clinical Center, National Institutes of Health, Bethesda, Maryland. All studies were performed during 1958 and, with infrequent exception, the large series of specimens were consecutive accessions to the laboratory.

was promptly obtained for culture. In a second experiment, 1,154 urine specimens sent for bacterial culture were also examined by the Griess test. A few days after this procedure was started, all specimens were additionally examined by the modified Griess test, so that 1,021 specimens were cultured and tested by two Griess methods. In a third study (of 336 female and 214 male job applicants), first voided urine specimens sent for routine urinalysis were also tested with the Griess reagent. Second specimens for culture were later obtained from some applicants with positive Griess tests or pyuria on the first specimen.

Routine Urinalysis: The first voided morning specimen from employment applicants was collected in a nonsterile cardboard container and was examined within two hours of collection. Specimens from patients were collected at varying times. Urinalysis consisted of determination of color, pH, sugar reaction, acetone and protein content, and of microscopic examination of sediment after centrifugation at 1,500 rpm for five minutes. Pyuria was considered to be present if there were five or more leukocytes per high power field.

Collection of Urine Specimens for Culture: In men, the glans penis was washed with benzalkonium chloride solution (Zephiran), and a midstream specimen was collected in a sterile container. In women, the vulva was cleansed with benzalkonium chloride solution, and by separating the labia a midstream specimen was collected in a sterile container. A few specimens were obtained by catheter.

Bacteriologic Examination: Specimens were cultured in thioglycollate, trypticase soy broth, blood agar, blood agar with phenylethyl alcohol, and desoxycholate media. Pour plates were made so that colony counts ranging from 10^1 to 10^6 bacteria/ml. were determined.

Griess Test: Approximately 1 ml. of the Griess reagent was added to 1 ml. of urine. The development of a pink or red color in a matter of seconds was considered to be a positive test. The modified procedure consisted of incubating 1 ml. of urine for one hour at room temperature with 0.5 ml. of a 10% solution of potassium nitrate before testing by the foregoing method.

Preparation of the Griess Nitrite Reagent: One and one-half grams of sulfanilic acid (chemically pure) were dissolved in 450 ml. of 10% acetic acid. This solution was added to a solution of 0.6 gm. alphanaphthylamine (chemically pure) in 60 ml. of boiling distilled water and filtered through Whatman No. 1 filter paper. Preparation required approximately 15 minutes. This combined reagent, now colorless, was stored in a tightly stoppered dark flask to prevent oxidation. The reagent in this form remained stable for from two to four weeks, and decomposition was detected by the appearance of a pinkish color in the solution.[4] The activity of the reagent was tested by adding a few drops to a few milliliters of 10% sodium nitrite solution and noting the development of a red color.

TABLE 1

Urine Cultures from 234 Patients* with Positive Griess Tests on Prior Urine Specimens

	No.	Per Cent
Greater than 100,000 bacterial colonies per milliliter	228	97.4
Less than 100,000 bacterial colonies per milliliter	6	2.6
	234	100.0

* These 234 patients contributed 293 urine specimens showing positive Griess tests out of 3,504 sent for routine urinalysis.

RESULTS

Frequency of Positive Urine Culture in Specimens Exhibiting a Positive Griess Test: Table 1 shows the results of culture of specimens of urine obtained from 234 patients whose previous specimen had given a positive Griess test. It is apparent that culture is almost invariably positive when the Griess test is positive. In six patients, however, the test was considered to be falsely positive. Positive specimens were obtained from two patients with phimosis in whom nitrite was detected on the glans penis, two patients from whom the urine was considered to be positive as a result of contamination from cotton sponges, and two patients ill with leukemia who were receiving antifolic acid therapy but had no evidence of urinary tract infection.

Frequency of Positive Griess Tests According to Quantitative Results of Culture: Among 377 urine specimens (Table 2) which contained greater than 10^5 bacterial colonies per milliliter, slightly more than one-half (192 of 377) gave a positive Griess test. Among 777 specimens with less than 10^5 colonies per milliliter, the Griess test was positive in only 28. Medical records of patients with these 28 urines were reviewed, and all were receiving antimicrobial treatment for urinary tract infection at the times the specimens were obtained. Furthermore, urine specimens at other times had contained greater than 10^5 bacterial colonies per milliliter.

Frequency of Positive Griess Tests According to Presence of Pyuria: Table 3 shows the results of the Griess test on urine specimens divided ac-

TABLE 2

Greiss Reactions in 1,154 Urine Specimens Submitted for Culture

	No.	Per Cent
Culture Positive ($> 10^5$ colonies per milliliter)		
Griess test *positive*	192	16.7
Griess test *negative*	185	16.0
Subtotal	377	32.7
Culture negatives ($< 10^5$ colonies per milliliter)		
Griess test *positive*	28	2.4
Griess test *negative*	749	64.9
Subtotal	777	67.3
Total	1,154	100.0

TABLE 3

Correlation Between Pyuria and Griess Test in Urine Specimens from 336 Female Job Applicants

	No.	Per Cent
Pyuria		
Griess test positive, culture positive	9	2.7
Griess test negative, culture positive	2	0.6
Griess test negative, culture negative	31	9.2
Subtotal	42	12.5
No pyuria		
Griess test positive, culture positive	4	0.3
Griess test positive, no culture information	4	1.8
Griess test negative, no culture information	286	85.4
Subtotal	294	87.5
Total	336	100.0

cording to the presence of pyuria. Among 42 specimens (13%) with pyuria, only nine, or about one-fifth, gave a positive Griess test, and all of these were positive on culture. Two specimens with pyuria had a negative Griess test and a positive culture, whereas 31 had both negative Griess tests and negative cultures. In the absence of pyuria the Griess test was rarely positive (eight of 294 specimens). Four of these eight specimens were examined by culture and all were positive. Pyuria was present in 25 (12%) of 214 urines from male job applicants, but only one had a positive Griess test. He was later found to have duplication of the ureters and a positive urine culture. None of the other 24 patients with pyuria had a positive culture. These data thus reveal a significantly higher frequency of positive Griess tests among pyuric patients, and agree with the previous findings that cultures are very frequently positive when the Griess test is positive.

Frequency of Positive Griess Test According to Bacterial Species Isolated from Urine: Table 4 shows the percentage of positive Griess tests among specimens with greater than 10^5 bacteria per milliliter on culture

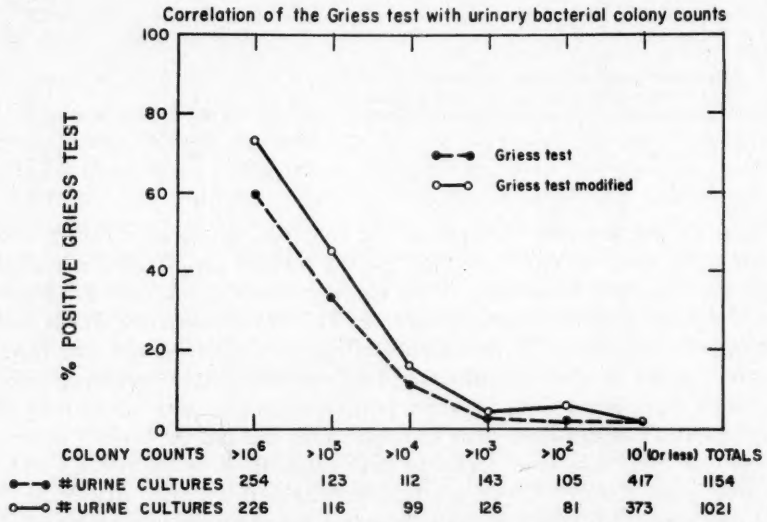
TABLE 4

Percentage of Positive Griess Tests According to Bacterial Species Isolated from Urine

	Positive Cultures* No.	Positive Griess Tests No.	Positive Griess Tests %
E. freundi	3	3	100.0
Paracolon species	20	15	75.0
E. coli	143	83	58.0
Pseudomonas species	20	11	55.0
Klebsiella-Aerobacter species	84	36	42.8
Staphylococcus species	9	1	11.1
Candida species	9	1	11.1
Streptococcus species	5	0	0.0
Salmonella species	1	0	0.0
Unidentified gram-negative species	12	0	0.0
	377	193	51.2

* Specimens yielding greater than 10^5 bacteria per milliliter.

according to the species (or predominant species) isolated (Table 2). It may be seen that, among bacteria found in 20 or more specimens, 42.8% to 75% gave positive Griess tests. The species giving the highest percentage of positive tests, in diminishing order of frequency, were *Escherichia freundi, Paracolon, Proteus, E. coli, Pseudomonas,* and *Klebsiella-Aerobacter.*



COLONY COUNTS	$>10^6$	$>10^5$	$>10^4$	$>10^3$	$>10^2$	10^1 (or less)	TOTALS
# URINE CULTURES	254	123	112	143	105	417	1154
# URINE CULTURES	226	116	99	126	81	373	1021

FIG. 1.

Frequency of Positive Griess Tests According to Colony Count of Bacteria in Urine: Figure 1 is a comparison of the percentage of positive Griess tests with the bacteria colony counts in the 1,154 specimens cultured (Table 2). There is a clear correlation of the number of bacteria per milliliter with the frequency of positive Griess tests. In specimens with greater than 10^6 bacteria per milliliter, 60% of tests were positive. In specimens with more than 10^5 but less than 10^6 bacteria per milliliter, 33% were positive. In specimens with colony counts greater than 10^4 bacteria per milliliter, only 12% were positive. When the available substrate (modified test) was increased, positive Griess tests were increased by about one-fourth (60 to 73%, and 33 to 45%—Figure 1) in urines with colony counts of 10^5 and 10^6.

COMMENT

These studies reveal that a positive Griess test almost invariably indicates a significant bacteriuria, due to any of several bacterial species which commonly cause urinary tract infection. A negative test, however, does not indicate lack of bacteriuria, for about one-half of urines with bacterial colony

counts greater than 10^5 per milliliter had negative Griess tests. These negative specimens were distributed among several bacterial species.

Kahler and Guze [6] have reported that the Griess test detects nitrite in concentrations of 0.1 μg./ml., and specimens which are bacteriologically positive and Griess-negative may have failed to reach this concentration of nitrite, for the following reasons:

1. Lack of sufficient substrate.
2. Lack of time for enzyme production due to frequent or continuous bladder emptying (as by catheter).
3. Diuresis, preventing concentration of nitrite to a measurable value.
4. Inhibition of metabolic activity of bacteria by antimicrobial treatment, acidification of the urine, etc.
5. Infection by a species or strain of bacteria that produces little or no nitrate reductase.

In regard to lack of substrate, data have already been presented that addition of nitrate and incubation at room temperature increases by approximately 25% the number of positive Griess tests. In corrollary studies we have found that only 104 (64%) of 162 specimens of urines from job applicants, and only 90 (45%) of 199 urines randomly selected from patients, contained as substrate nitrate detectable by the method of Blom, as cited by Feigl.[7]

There is also evidence that suggests that negative tests were related to passage of urine before sufficient time for production of enzyme. It has been shown [6] that from two to five hours are required by a large number of bacteria (greater than 1,000,000 colonies/ml.) to produce detectable nitrite. Some of our patients with negative Griess tests had indwelling catheters. Nine job applicants who had Griess-positive, culturally positive first voided urines submitted afternoon specimens. Of these, only four were positive, despite the fact that cultures of afternoon specimens were still positive.

That urinary retention in the bladder for a period of time is not always essential to production of nitrite is suggested by our finding positive cultures and Griess tests of urine obtained by ureteral catheterization from the kidney pelves of two patients. It would thus be of interest to know if lesions of the kidney parenchyma produce this enzyme, and how metabolic activity of bacteria is influenced by their location in vivo.

It seems probable that the value of the test in the diagnosis of urinary tract infection might be improved by concentrating the urine specimen 10 or 20 times before testing. Since nitrite is relatively stable, there is reason to believe this can be accomplished. In addition to whatever value the test may have in diagnosis, it provides a relatively sensitive chemical test of bacterial metabolism in vivo, and a detailed examination of its relation to the physiologic and pathologic changes in renal and other urinary tract infection is worthy of further study.

Summary

1. A positive Griess test for nitrites in urine was associated with a positive urine culture (colony count greater than 100,000/ml.) of a subsequent specimen in 97.4% of 234 patients.

2. However, among 377 urine specimens with positive bacterial cultures, only 50.8% exhibited a positive Griess test.

3. The Griess test was positive in nine of 42 urine specimens from female job applicants with pyuria. All nine Griess-positive urines yielded positive cultures, whereas only two of the remaining 33 urines had positive cultures.

4. The percentage of positive Griess tests on culturally positive urine varied according to the species of bacteria isolated.

Summario in Interlingua

Le desiderato de un convenibile methodo pro le detection in massa de infection del vias urinari inspirava un re-evalutation del test de nitrito de Griess. Nitritos es formate in le urina como resultato del reduction bacterio-enzymatic de nitratos e pote esser detegite gratias al production de un color rubie post le addition del reagente de Griess (que es un solution continente acido acetic-sulfanilic e alphanaphthylamina). Specimens de urina esseva obtenite ab 336 feminin sollicitantes de empleo e ab patientes pro le quales urinanalyses standard o culturationes bacterial de urina esseva effectuate (3.504 e 1.154 specimens, respectivemente). Novanta-septe pro cento del patientes qui habeva un positive test de Griess in specimens de urina submittite pro le urinanalyse habeva etiam un positive cultura (de plus que 100,000 colonias per ml) in un secunde specimen. Studios del urinas ab le sollicitantes de empleo corroborava le conclusion que quando le test de Griess es positive il ha quasi invariabilemente un positive culturation urinari. Tamen, solmente 51% de urinas con positivitate del cultura bacterial resultava in un positive test de Griess. Le obtention de negative tests de Griess in culturalmente positive urinas pare esser relationate a plure factores possibile: Un inadequate substrato de nitrato ab fontes alimentari, variationes in le production de reductase de nitrato per differente species de bacterios, insufficiente intervallos de tempore pro le action enzymatic (per exemplo in patientes con catheteres in sito), e "falsemente positive" culturation urinari.

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THE ANTITHROMBOTIC PROPERTIES OF COUMARIN DRUGS * †

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INTRODUCTION

IN recent years, coumarin drugs have played an important role in the treatment of thrombo-embolic disease. Despite the widespread use of these drugs, the exact mechanism by which they inhibit thrombosis is unknown.

Since anticoagulant activity, as measured by in vitro methods, is not necessarily synonymous with antithrombotic activity, a laboratory test which approximates in vivo clotting conditions would be extremely useful. Blood coagulates when it is placed in a glass tube because the "glass or contact factor" is activated and initiates clotting.[1] Blood normally remains fluid within the blood vessels and clots more slowly in a siliconized tube because this factor presumably is inactive. The clotting surface of a silicone coated glass tube simulates the endothelial surface of a blood vessel more closely than does a plain glass surface.[2] Silicones are synthetic polymers which interact with water and glass to form a water repellent film on the surface of a tube. It is thought that this surface in some manner interferes with the activation of the glass or contact factor [1] and the formation of plasma thromboplastin is delayed.

If significant inhibition of intravascular clotting is effected by coumarin therapy, comparable inhibition of clotting in silicone coated glass tubes might be expected. Experience indicates that such is the case. Moloney, Murphy, and Harrington [3] and later, Margulies and Barker [4] noted marked prolongation of the whole blood clotting time in silicone coated glass tubes following dicumarol therapy. In some instances, the blood did not clot within 24 hours. Interestingly, the degree of prolongation of the whole blood silicone clotting time did not consistently coincide with the amount of depression of prothrombin activity as measured by the one-stage prothrombin time.

In addition to depressing the prothrombin and factor VII levels, coumarin drugs are known to cause depression of factor IX (plasma thromboplastin component) and factor X (Stuart-Prower).[5-13] Since the latter two

* Received for publication June 27, 1960.
Presented at the Forty-first Annual Session of The American College of Physicians, San Francisco, California, April 5, 1960.
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† This work was supported by research grants from the American and Iowa Heart Associations and the National Institutes of Health.
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factors are needed for the generation of normal plasma thromboplastin, it seems reasonable that deficiencies of factors IX and X would be reflected in prolongation of the silicone clotting time and presumably in comparable inhibition of intravascular clotting. The following studies were performed to determine what clotting factor deficiencies were associated with prolongation of the whole blood silicone clotting time in patients treated with coumarin drugs.

Methods and Materials

Detailed coagulation studies were performed on 28 patients who received either bishydroxycoumarin (dicumarol) or warfarin sodium (Coumadin) by the oral route. These patients had a variety of thrombo-embolic diseases including occlusive coronary atherosclerosis. Both out-patients and hospitalized patients were included in the study. The period of anticoagulant therapy varied from three days to three years.

Silicone coated glass tubes were prepared by treating glass clotting tubes (7.5 cm. by 1 cm.) with Dri-Film (General Electric Company). One part of Dri-Film was dissolved in four parts of petroleum ether. Six applications of the silicone preparation were made to new tubes before they were used. Following each application, the tubes were allowed to dry, then washed with tap water, rinsed with distilled water, and dried in an oven at 100° C. After each use, the tubes were thoroughly washed in Haemo-Sol solution and rinsed with tap water and distilled water. When the tubes were completely dry, two additional coats of Dri-Film were applied. Eighteen gauge stainless steel needles were coated once with Monocote (Armour-Arquad) to produce a non-wettable surface. Blood for the whole-blood clotting times was collected through a piece of polyvinyl tubing which was connected to a Monocote treated needle by a nylon adapter. This arrangement eliminated the need for syringes and decreased activation of the glass or contact factor. Blood for the other clotting studies was collected from a different vein by the two-syringe technique. Particular care was used in the performance of venipunctures since the introduction of tissue fluid invalidates the results of the silicone clotting time.

The whole blood clotting times were determined by a modified Lee and White method [14] at a temperature of 37° C. One milliliter of blood was allowed to run into several dry silicone coated and plain glass tubes. The time required for formation of a complete fibrin clot in the third tube was taken as the whole blood clotting time. The normal range in plain glass tubes was 5 to 14 minutes. The normal range in silicone coated glass tubes was 25 to 45 minutes. The thromboplastin generation test was performed by the method of Connor and Carter,[15] a modification of the method of Biggs and Douglas.[16] Attempts were made to correct all abnormal thromboplastin generation by the addition of normal, factor IX-deficient, and factor X-deficient sera. The serum component of the incubation mixture contained

TABLE 1

Case	Diagnosis	Period of Anti-coagulant Therapy	Whole Blood Clotting Time (Glass)	Whole Blood Clotting Time (Silicone)	1-Stage Pro-thrombin Time Pt./Cont. Sec.	Accelerator Activity (% Normal)	2-Stage Pro-thrombin (% Normal)	Thrombo-plastin Generation (% Normal)	Deficient Factor in TGT
1	Myocardial inf.	4 months	17′	No clot 2 hours	28.2/13	74	9	0	IX & X
2	Myocardial inf.	6 months	7′ 25″	33′ 30″	14.8/13	57	28	100	None
3	Myocardial inf., claudication	3 days	5′ 50″	65′ 50″	26/13.2	55	48	0	X
4	Basilar art. insuffic.	6 days	7′ 10″	No clot 2 hours	22/12.8	81	24	0	X
5	Myocardial inf.	10 days	7′	86′ 5″	16.8/13	87	21	0	X
6	Cerebral thrombosis	3 years	17′ 55″	No clot 2 hours	30.2/12.8	100	8	0	X
7	Thrombophlebitis	4 days	8′ 20″	No clot 2 hours	39.2/15	57	19	0	IX & X
8	Thrombophlebitis	5 days	15′ 5″	No clot 2 hours	31.8/15	80	19	0	IX & X
9	Cerebral vascular insuffic.	2 months	12′ 15″	No clot 2 hours	32.6/15	51	24	0	IX & X
10	Cerebral vascular insuffic.	6 months	14′ 20″	78′ 55″	26.8/15	78	26	6	IX & X
11	Myocardial inf.	3 years	14′ 25″	40′ 15″	28.5/15	27	24	100	None
12	Thrombophlebitis	8 days	14′ 20″	No clot 2 hours	25.8/14.8	70	9	0	IX & X
13	Myocardial inf.	1 year	16′ 40″	No clot 2 hours	27.2/15	58	10	0	IX & X
14	Normal subject	3 days	7′ 50″	65′ 25″	14.6/12.8	89	54	13	X
15	Normal subject	6 days	7′ 20″	No clot 2 hours	19.2/13	80	20	0	IX & X
16	Thrombophlebitis	23 days	14′ 40″	No clot 2 hours	26.4/13.8	45	10	0	IX & X
17	Thrombophlebitis	6 days	9′	No clot 2 hours	32.2/13.8	88	21	28	X
18	Coronary insuffic.	3 weeks	16′ 25″	No clot 2 hours	20.4/13.8	103	39	0	IX & X
19	Myocardial inf.	9 days	6′ 50″	54′	19.4/13.8	93	26	0	IX & X
20	Cerebral thrombosis	10 days	6′ 15″	57′	20.2/13.8	82	22	0	IX & X
21	Cerebral embolus	20 days	10′ 45″	No clot 2 hours	29.4/13.8	45	11	0	IX & X
22	Cerebral vascular insuffic.	4 days	10′ 30″	No clot 2 hours	29/13.6	98	22	24	IX & X
23	Myocardial inf.	2 weeks	10′ 30″	No clot 2 hours	25.3/13.8	25	9	0	IX & X
24	Thrombophlebitis	14 days	16′ 30″	No clot 2 hours	26.6/13.6	54	9	0	IX & X
25	Aortic thrombosis (post-endarterectomy)	6 days	9′	85′	20.2/13.8	83	21	0	IX & X
26	Thrombophlebitis	1 month	9′ 30″	66′	20/13.8	103	24	0	IX & X
27	Acute coronary insuffic.	4 days	11′ 45″	No clot 2 hours	25.6/13.8	50	26	0	IX & X
28	Thrombophlebitis	12 days	9′	No clot 2 hours	20.4/13.4	103	11	0	IX & X

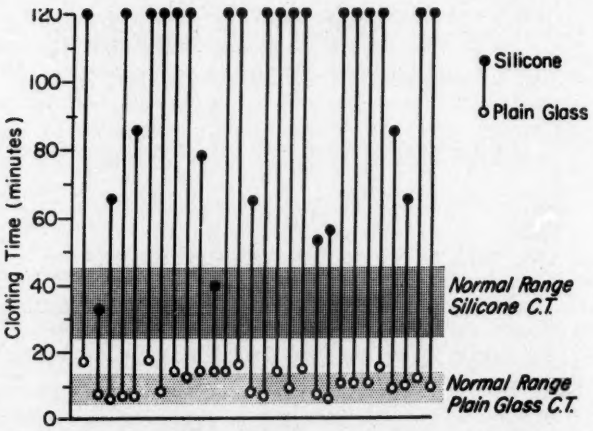

FIG. 1. Whole blood clotting times in plain glass and in silicone coated tubes. The vertical line connects the values for a given patient.

equal quantities of the patient's serum and the "correcting" serum. These deficient sera were obtained from patients with congenital deficiencies of the respective factors.

Prothrombin activity was measured by the Quick method [17] using Permoplastin as the source of thromboplastin. Prothrombin levels were measured by the two-stage method of Ware and Seegers.[18] Accelerator activity was measured by the method of Carter and Warner.[19] Abnormal accelerator activity in these patients was corrected by the addition of normal serum to the incubation mixture. Previously, such a correction was believed to indicate a factor VII deficiency. In view of the recent demonstration of a new serum factor, factor X or the Stuart-Prower factor,[10] we cannot rule out the possibility that abnormal accelerator activity, as measured by this method, may indicate factor X as well as factor VII deficiencies.

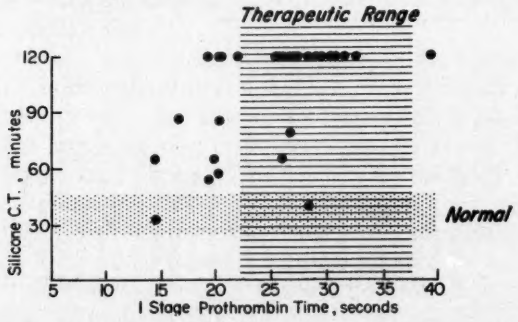

FIG. 2. Correlation between the one-stage prothrombin time and the whole blood silicone clotting time. Each dot represents the value for a given patient.

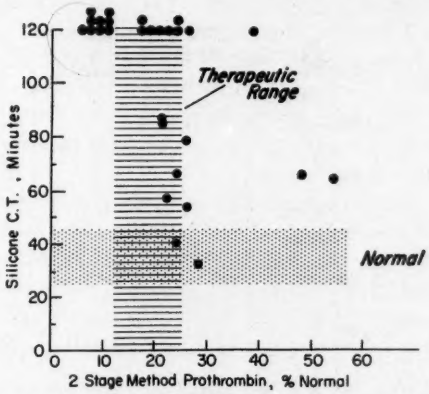

FIG. 3. Correlation between the prothrombin level (as measured by the two-stage method) and the whole blood silicone clotting time.

RESULTS

The whole blood silicone clotting time was prolonged in 26 of 28 patients, while in contrast, the clotting time in plain glass tubes was slightly prolonged in only 10 cases. Two patients had normal silicone clotting times while 18 had normal clotting times in plain glass tubes (Table 1, Figure 1). The silicone clotting time was greater than two hours in 18 cases and between 50 and 120 minutes in eight instances. In a few cases, the whole blood silicone clotting times of the coumarin treated patients were longer than 24 hours.

In Figure 2, the correlation between the silicone clotting time and the one-stage prothrombin time values is shown. Sixteen patients had one-stage prothrombin times from 1-1/2 to 2-1/2 times the control value. Eleven patients had one-stage prothrombin times below this range. Only

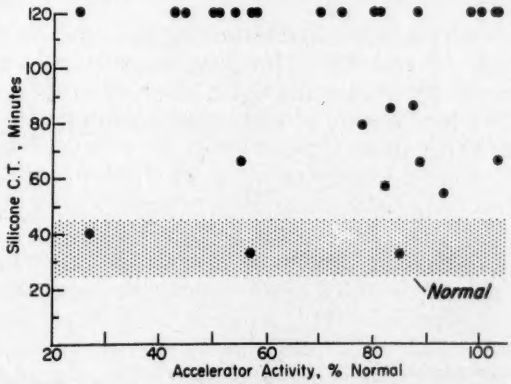

FIG. 4. Correlation between accelerator activity and the whole blood silicone clotting time.

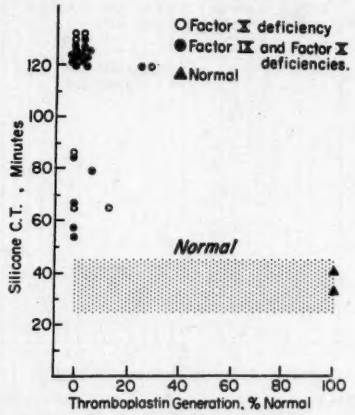

FIG. 5. Correlation between thromboplastin generation and the whole blood silicone clotting time.

one patient had a value above this range. With one exception (case 11), all patients with one-stage prothrombin times within the so-called therapeutic range (1-1/2 to 2-1/2 times the control value) had prolonged silicone clotting times. There were 10 patients with prothrombin times below the therapeutic range who had prolonged silicone clotting times.

The correlation between the silicone clotting time and prothrombin levels is shown in Figure 3. The prothrombin levels were measured by the two-stage method which measures only prothrombin and is not influenced by factor VII or factor X deficiencies as is the one-stage prothrombin time. It can be seen that prolongation of the silicone clotting time frequently, but not consistently, correlates with depressed prothrombin levels.

It was found that there was little or no correlation between accelerator levels and prolongation of the silicone clotting time. These results are shown in Figure 4.

All patients with prolonged silicone clotting times had impaired thromboplastin generation (Figure 5). This impairment resulted because all patients had factor X deficiencies and, in addition, 19 of them had factor IX deficiencies. The two patients with normal thromboplastin generation had normal silicone clotting times.

TABLE 2

	Normal	Case 9	Case 11
Clotting time (glass)	5–14′	12′ 15″	14′ 25″
Clotting time (silicone)	25–45′	No clot 3 hours	40′ 15″
1-stage prothrombin	13–15 sec.	32.6 sec.	28.5 sec.
2-stage prothrombin	100%	24%	24%
Accelerator activity	100%	51%	27%
Thromboplastin generation	100%	0% Factors IX and X deficiency	100%

In Table 2, the contrasting clotting results of two patients are shown. In the one instance (case 9), the silicone clotting time was markedly prolonged and the thromboplastin generation defective. In the other patient (case 11) values for both of these tests were normal. Yet, both patients had prothrombin and accelerator levels that are usually regarded as being within the therapeutic range.

No difference was found between bishydroxycoumarin and warfarin in the effect upon depression of clotting factors. Only one patient died during our period of observation. He was one of two patients with normal silicone clotting times and normal thromboplastin generation tests. This patient had a history of two myocardial infarctions. Death was sudden and probably cardiac in origin. An autopsy was not performed.

Discussion

Our studies indicated that factor IX and factor X deficiencies correlated directly with prolongation of the whole blood silicone clotting time in patients receiving coumarin drugs. There was no consistent correlation of factor VII or prothrombin levels with prolongation of the silicone clotting time. These results strongly suggest that prolongation of the silicone clotting time in these patients depends upon defective thromboplastin generation rather than depressed prothrombin and accelerator levels.

It is difficult to assess the exact role that the various clotting factor deficiencies play in the inhibition of thrombosis. Sise et al.[13] believe that the prothrombin level rather than factor VII activity is of greater significance both for production of bleeding and thrombosis in coumarin treated patients. This view does not take into account the part played by factor IX and factor X deficiencies. In our experience, the factor IX and factor X levels usually paralleled the prothrombin levels. This is not always the situation as shown by cases 2 and 11 (Table 1). It appears that low concentrations of prothrombin and/or factor VII can produce bleeding. However, the levels of these factors resulting from the therapeutic use of coumarin drugs may not necessarily prevent thrombosis.

Wessler has found little or no protection against intravascular thrombosis in coumarin treated animals with low prothrombin and factor VII levels.[20, 21] In his more recent animal studies, the results indicate that intravascular thrombosis is inhibited in animals when there is a deficiency in certain clotting factors necessary for thromboplastin generation.[22, 23]

Douglas[11] has hypothesized that the primary role of coumarin drugs may be in the control of intrinsic thromboplastin formation. Our work supports these earlier speculations. The antithrombotic effect of coumarin drugs may result mainly from the production of a hemophilioid state. It may well be that, with the use of coumarin drugs, controlled depression of clotting factors necessary for plasma thromboplastin generation should be the therapeutic goal rather than controlled depression of prothrombin and factor VII levels.

Summary

Coagulation studies were performed on 28 patients who were receiving coumarin drugs for variable periods of time. These studies included the whole blood clotting times observed in siliconized tubes and the thromboplastin generation test (TGT). All patients with prolonged silicone clotting times had abnormal thromboplastin generation. No consistent relationship was found between the whole blood silicone clotting time and the prothrombin or factor VII levels. Our studies indicated that factor IX and factor X deficiencies correlate directly with prolongation of the silicone clotting time in patients receiving coumarin drugs. Such deficiencies, rather than depressed prothrombin and factor VII levels, may be largely responsible for the antithrombotic activity of these drugs.

Acknowledgment

We wish to thank Doctors John B. Graham and Charles L. Johnston, Jr. of the University of North Carolina School of Medicine who kindly supplied us with factor X (Stuart-Prower) deficient serum.

Summario in Interlingua

Le mechanismo per le qual drogas coumarinic preveni thromboses non es cognoscite. Patientes tractate con dicumarol manifesta frequentemente un frappante prolongation del tempore coagulatori de sanguine integre in tubos siliconisate, lo que non pote esser explicate satisfactorimente per le nivellos observate pro prothrombina e factor VII. Isto suggere que altere deficientias de factores coagulatori ha un rolo importante. In su relation al phenomeno del coagulation, le endothelio vascular es melio simulate per tubos de vitro siliconisate que per vitro ordinari. Per consequente, deficientias in factores de coagulation que causa un prolongation del tempore de coagulation in vitro siliconisate es possibilemente de importantia special in le inhibition de thromboses.

Detaliate studios de coagulation esseva effectuate in 28 patientes qui recipeva dicumarol o warfarina a natrium (Coumadina). Le studios includeva le tempores prothrombinic uni- e bi-phasic, le tempores de coagulation de sanguine integre in vitro ordinari e siliconisate, determinationes del acceleratores (factores V e VII), e le generation de thromboplastina. Seros normal, seros deficiente in factor IX (componente thromboplastinic del plasma), e seros deficiente in factor X (Stuart) esseva empleate pro corriger anormal tests de generation de thromboplastina.

Le tempore coagulatori de sanguine integre in vitro siliconisate esseva prolongate in 26 patientes, durante que solmente 10 casos monstrava un leve prolongation de ille tempore in vitro ordinari. Le tempore coagulatori in vitro siliconisate esseva plus que duo horas in 18 casos e inter 50 e 120 minutas in octo. Le valor medie in casos de controlo es $33{,}5 \pm 6{,}2$ minutas. Omne le patientes con prolongation del tempore coagulatori in vitro siliconisate habeva defectos del generation de thromboplastina e deficientias de factor X. Dece-novem patientes habeva etiam deficientias de factor IX. Nulle relation de character systematic existeva inter le tempore coagulatori de sanguine integre in vitro siliconisate e le valores de prothrombina o de factor VII. Dece-sex patientes habeva uni-phasic tempores prothrombinic de inter un vice e medie e duo vices e medie le valor de controlo. Dece-un patientes habeva uni-phasic tempores prothrombinic infra ille nivello.

Nostre studios indica que le deficientia de factor IX e illo de factor X es correlationate directemente con le prolongation del tempore coagulatori in vitro siliconisate in le caso de patientes sub tractamento con drogas coumarinic. Tal deficientias plus tosto que deprimite nivellos de prothrombina e de factor VII es possibilemente responsabile in grande mesura pro le activitate antithrombotic de iste drogas.

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POST-MICTURITION SYNCOPE *

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CARDIOVASCULAR collapse has been associated with forced expiration against a closed glottis (Valsalva's maneuver) since ancient times. Galen, Valerius Maximus, and Appianus of Alexandria were all aware that convulsions and death could be caused by breath-holding.[1] Scientific investigation of this phenomenon was not done until Eduard Weber noted in 1850 that fainting and obliteration of the peripheral pulse occurred during this maneuver. Subsequently it was discovered that Valsalva had previously described this phenomenon during the 18th century. During the late 19th and 20th centuries many articles were written on the deliberate application of this maneuver to test the competency of the cardiovascular system and to elucidate the maneuver's mechanism of action. Syncope associated with the use of the bedpan,[2, 3] with cough,[4] and, more recently, with micturition,[5] has stimulated clinical interest in the Valsalva maneuver in the pathogenesis of conditions which are associated with straining. The major emphasis has been placed on phase II of Valsalva's maneuver, described below, as the cause of the cardiovascular collapse.

The dynamics of Valsalva's maneuver have been described by several investigators [6-8] and have been divided into four phases. Phase I begins with the onset of straining and consists of a rise in blood pressure associated with a forceful expulsion of blood from the lungs into the left side of the heart, increasing cardiac output. This rise in blood pressure is followed shortly by a marked fall, which is the beginning of phase II. Phase II continues until the release of the strain and is manifested by a narrow pulse pressure with a rising diastolic pressure resulting from the precipitous fall in cardiac output and the concomitant rise in peripheral resistance. Upon release of the strain—the beginning of phase III—the dynamics of phase II are exaggerated due to the absorption of the right ventricular output by the sudden expansion of the previously compressed vascular tree of the lung, which momentarily decreases further the venous return and output of the left ventricle. Phase IV follows immediately with a second rise in blood pressure above control levels, a consequence of the increasing cardiac output and the maintenance of the increased peripheral resistance. This is the so called "over-shoot." This blood pressure elevation activates the carotid sinus and the aortic arch reflexes, which cause a diminution in peripheral resistance and a bradycardia.

* Received for publication May 23, 1960.

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We have observed three cases of syncope associated with micturition in healthy adult males. Upon careful study of these cases it would appear that the mechanism of syncope is the result of exaggerated carotid sinus and aortic arch reflexes with marked vagotonia associated with phase IV of Valsalva's maneuver rather than with the previously ascribed phase II.

Case Reports

Case 1. G. R., a 19-year-old Navy enlisted man, entered the Sandia Base Army Hospital because of fever, generalized aching, and a sore throat. The patient had been exposed to hepatitis and had received gamma globulin injections prophylactically one week prior to admission. Past medical history and family history were noncontributory. Findings on physical examination were completely within normal limits except for a temperature elevation to 100° F. and a mildly injected pharynx. Pressure on the carotid sinus did not cause significant slowing of the heart. Complete blood count, erythrocyte sedimentation rate, urinalysis, serology, liver function tests including bromsulfalein and serum glutamic-oxalacetic transaminase, and heterophile antibody titer determinations were all found to be normal. A throat culture revealed beta-hemolytic streptococci, group A. Chest x-ray was normal. An electrocardiogram and Master's two-step exercise test were normal.

Because of the results of the throat culture, the patient received Bicillin, 1,200,000 units, intramuscularly. On the third day of hospitalization, the patient felt well and was afebrile. On the morning of the fourth day, breakfast was withheld for blood chemistries. Upon arising from bed the patient went to the latrine to void. After finishing the act of micturition, he suddenly felt faint and collapsed. At this point, one of us (G. B. P.) was called to see the patient. He was found lying on his back in an unconscious state at the urinal. His skin was cold and moist. The pupils were dilated. The blood pressure was unobtainable. Auscultation of the heart revealed a grossly irregular rhythm with a rate of about 50. It was noted at this time that all of the urine was in the urinal, none on the floor or on the patient. An electrocardiogram, taken after the patient had been removed to a bed, revealed atrial fibrillation with a high degree of A-V block and unifocal premature ventricular beats at a rate of 50/min. (Figure 1A). At this time the patient regained consciousness and was aware of a peculiar sensation in the left side of his chest. It was decided to administer atropine; but before it could be obtained, the heart beat spontaneously converted to a sinus rhythm at a rate of 70 with a PR interval of 0.19, ten minutes after the onset of the episode. Blood for glucose, serum calcium, and serum potassium values was drawn while the heart was fibrillating. The results were all normal.

Further studies were done to determine the cardiovascular and electrocardiographic responses to Valsalva's maneuver (forced expiration from inspiratory midposition against 40 mm. of mercury pressure for 15 seconds in a supine position) before and after the intravenous injection of 2 mg. atropine sulfate. The blood pressure response was measured with a mercury manometer cuff. The maneuver was repeated several times to obtain numerous readings in each phase. Average readings are shown in Table 1.

The electrocardiogram was recorded continuously, employing the three standard leads, the unipolar limb leads, and esophageal leads E 20–30. Changes occurred in the rate, the rhythm, and the T vector. Ten to 15 seconds after the onset of strain, an increase in heart rate to approximately 140 occurred. Six seconds after the patient had stopped straining, the rate slowed abruptly. With the onset of bradycardia (phase IV), there was a brief period of sinus arrest followed by a nodal rhythm which persisted usually for two or three minutes, but at times for five minutes (Figure 1B). The change in locus of the pacemaker was confirmed by esophageal leads.

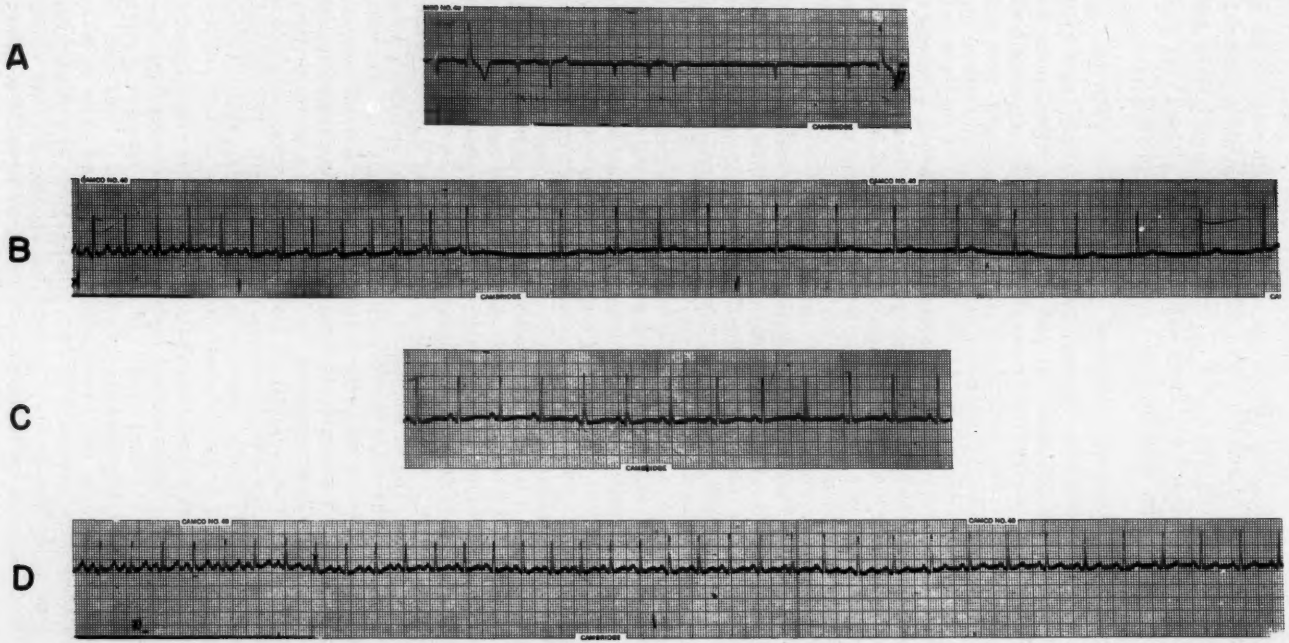

FIG. 1. Electrocardiographic tracings of Case 1 (Patient G. R.). A. Lead aVL taken during the episode of syncope. Atrial fibrillation with a high degree of block and ventricular premature beats are seen. B. Electrocardiographic response to Valsalva's maneuver (lead II). Heavy horizontal line at bottom of graph indicates the terminal portion of the period of strain. T wave inversion occurs for several beats prior to the period of sinus arrest, which is followed by a nodal rhythm. C. Tracing taken five minutes after Valsalva's maneuver on another trial. Sinus rhythm is present but T wave inversion persists. D. Electrocardiographic response to Valsalva's maneuver (lead II) after atropine sulfate, 2 mg. intravenously. Heavy line at bottom of graph indicates period of strain. The T wave inversion, sinus arrest, and nodal rhythm are not produced.

During the period of strain (phase II) the T vector increased in magnitude but did not change direction. Upon the release of the strain, the T vector immediately diminished in magnitude and changed direction from a control of 60° to −40° at its maximum (inverted in leads II, III, and aVF). The T vector change always took place prior to the nodal rhythm (Figure 1B). Its return to control configuration was variable and bore no fixed relation to the change in rhythm, at times persisting for from five to six minutes (Figure 1C). The ventricular gradient was calculated and showed a significant change in direction, signifying a primary T wave change.[9] After atropinization, the reflex bradycardia, the changes in rhythm, and the T vector change were abolished (Figure 1D). However, the blood pressure responses were even more marked, as has been previously described.[6, 10]

TABLE 1

Blood Pressure Readings in Case 1 Taken During the Valsalva Maneuver Before and After the Administration of Atropine

	Control	Phase I	Phase II	Phase III	Phase IV
Without atropine	115/65	118/70	110/100*	100/80*	135/80
Atropine 2 mg. I.V.	105/70	110/70	Unobtainable by auscultation*	Unobtainable by auscultation*	160/90

* The patient had no symptoms at any time during phases II and III. Twelve attempts were made without atropine and on four occasions the blood pressures were unobtainable. Four attempts were made using atropine.

Comment: This healthy young male had an episode of syncope following the completion of the act of micturition and not during the period of strain. In the midst of the episode, he was found in shock with atrial fibrillation, a high degree of A-V block, ventricular premature beats, and a heart rate of 50. Sinus arrest, nodal rhythm, and T vector changes were produced in phase IV of Valsalva's maneuver. These changes were abolished by atropine.

Case 2. J. K., a 30-year-old Army supply officer, entered the Sandia Base Army Hospital because of syncope which had occurred four hours prior to admission. The patient had been perfectly well until the previous evening, when he noted an "upset stomach" and passed two loose stools. He was awakened from sleep at about 4:00 a.m. by the desire to micturate. After completing the act of micturition, he took one step away from the toilet and collapsed in the bathroom doorway, falling to the floor. He regained consciousness in about one minute and returned to bed. He felt well the following morning and went to work. His superior officer, upon hearing of the incident, requested a physical examination. Past medical history and family history were noncontributory. A complete physical examination showed findings within normal limits. Pressure on the carotid sinus did not cause significant slowing of the heart rate. Complete blood count, erythrocyte sedimentation rate, serology, urinalysis, fasting blood glucose, cholesterol, and uric acid data were normal. Chest x-ray was normal. An electrocardiogram revealed inverted T waves in leads II, III, aVF, V_5 and V_6. These changes reverted to normal on the following day. Master's two-step exercise test was normal. The electrocardiographic response to Valsalva's maneuver was studied as described in case 1. Changes occurred in the rate, the rhythm, and the T vector. The changes in rate were similar to those which occurred

in case 1. Periods of sinus arrest and nodal rhythm followed the release of strain. The nodal rhythm was of five to 10 beats' duration but on one occasion persisted for five minutes. The T vector changed from a control of 25° to − 35° at its maximum, became inverted in leads aVF and II, and returned to normal within ten seconds. The T vector change always preceded the bradycardia and change in rhythm. A change in the ventricular gradient confirmed the fact that the T wave change was primary.[9]

Comment: This patient had syncope following micturition and not during the period of strain (Valsalva's maneuver), as illustrated by his collapse in the doorway of the bathroom. An electrocardiogram taken several hours later revealed T wave changes suggestive of injury to the posterolateral wall. These reverted to normal the following day and were not accompanied by laboratory data suggestive of death of tissue. They were not reproduced by the two-step exercise test, but were reduplicated in phase IV of Valsalva's maneuver. Sinus arrest and nodal rhythm were also observed during this phase of Valsalva's maneuver.

Case 3. C. D., a 40-year-old Army officer, entered the Sandia Base Army Hospital because of a syncopal episode. On the night prior to admission he had gone to bed at 10:00 p.m. and slept for about two hours. He awoke at midnight and went to the bathroom to micturate. Following the act of micturition, he turned around to turn out the bathroom light, and while reaching for the light he fell to the floor unconscious. He was completely unconscious for a period of ten minutes. After this episode he returned to bed but continued to feel weak. Because of the persistent weakness he sought medical attention. Past medical history and family history were noncontributory. Complete physical examination showed normal findings. Pressure on the carotid sinus did not cause significant slowing of the heart. Complete blood count, erythrocyte sedimentation rate, urinalysis, serology, and chest and skull x-rays were within normal limits. The electrocardiogram taken on admission was normal. An electroencephalogram was normal. On performing Valsalva's maneuver, sinus arrest occurred with a nodal escape rhythm which persisted for 15 seconds. The T vector diminished in magnitude but did not change in direction.

Comment: This patient had syncope following micturition and not during the act of strain as illustrated by his turning around to reach for the light. Initially, he was admitted to the neuropsychiatric service where the seriousness of the symptoms prompted skull films and an electroencephalogram. On performance of Valsalva's maneuver, sinus arrest and a nodal rhythm occurred.

Control Studies: The electrocardiographic response to Valsalva's maneuver was studied in 20 healthy adult males between the ages of 18 and 32. None of these men had cardiovascular disease or a history of syncope. In 18 of them a normal response was elicited without evidence of T wave inversion or an arrhythmia in phase IV. One subject showed an occasional nodal beat in phase IV but no consecutive nodal beats. In the other subject a period of sinus arrest and one nodal escape beat appeared. This was associated with a momentary T vector change (+ 25° to − 30°), which disappeared in the following beat.

Comment: Only one of 20 consecutive control subjects showed abnormalities similar to those seen in our cases. These were of short duration.

Discussion

Micturition syncope is not a rare experience in healthy young adults.[5] Heretofore, the diminished cardiac output of phase II of Valsalva's maneuver has been considered to be the cause of the syncope. However, in all three of our cases the act of micturition (and hence the strain) was completed prior to the onset of syncope, clearly placing the time of the syncope in phase IV. In addition, in case 1, the only case to our knowledge to be observed during the syncopal episode, atrial fibrillation with a high degree of A-V block was found during the attack.

Several interesting phenomena were observed during the experimental Valsalva's maneuver in our cases. First, although obliteration of blood pressure occurred in phase II, no symptoms or significant electrocardiographic changes except an increase in rate were noted at this time. Second, a primary T wave change occurred early in phase IV, prior to the reflex bradycardia, in two of the three cases. Third, the reflex bradycardia in two of the three cases was severe enough to cause sinus arrest and a nodal escape rhythm which was constant and persisted for as long as five minutes. In the third case nodal rhythm alone was noted. It is of the utmost importance to note that both the T wave change and the arrhythmia were abolished by atropine, but the blood pressure changes were exaggerated with a more marked "over-shoot," implicating acetylcholine rather than the changes in cardiac work as the mediator of the abnormal response.

It has been demonstrated that acetylcholine produces arrhythmias and changes in the process of repolarization in the canine myocardium, significantly altering the T wave of both the atrium and the ventricle.[11, 12] Experimentally, T wave changes have been shown to occur prior to the onset of the chronotropic effect of acetylcholine.[12] The arrhythmias most commonly observed were (1) varying degrees of A-V block, (2) cardiac standstill, (3) atrial fibrillation, and (4) occasional ventricular fibrillation. In the presence of anoxemia, the susceptibility of the canine myocardium to the effects of acetylcholine is augmented, invariably producing cardiac arrest followed by a period of atrial fibrillation.[13] Diminished coronary perfusion and myocardial anoxemia are present during phase II of Valsalva's maneuver, even producing typical angina pectoris in susceptible individuals,[7] and apparently sensitizing the myocardium to the effects of acetylcholine in phase IV. The similarity of these experimental results to our cases is apparent.

The diminished cardiac perfusion and anoxemia of phase II with an excess of acetylcholine in phase IV, producing temporary cardiac arrest and cardiovascular collapse followed by an arrhythmia, apparently is the mechanism of syncope following micturition. Although the syncope was not reproduced by the experiments with Valsalva's maneuver, hypersensitivity of the autonomic reflexes was clearly demonstrated by the T vector changes,

sinus arrest, and nodal rhythm. The response to Valsalva's maneuver in our 20 control subjects and in 122 control subjects studied by Halpern and associates [3] did not show significant arrhythmias or T vector changes in phase IV. This would indicate that people who are subject to syncope associated with micturition are either hypersecreting or are hypersensitive to acetylcholine as compared to the general population despite the absence of hypersensitivity of the carotid sinus. Invariably a period of recumbency has preceded the syncopal episode.[5] Possibly this further sensitizes the autonomic nervous system, causing a more prolonged arrest with syncope. A wider application of this mechanism in sudden unexplained deaths associated with Valsalva's maneuver, such as those on the bedpan [2] and possibly during certain phases of anesthesia, is apparent. We are currently investigating the latter possibility.

The persistence of the T wave changes several hours after the syncope in case 2 was a most unusual finding. These could be mistaken for ischemic T wave changes which, however, would be unlikely in the presence of a normal Master's two-step test. These same changes were reproduced by Valsalva's maneuver.

Summary

1. Three cases displaying syncope associated with micturition have been reported, in one of whom atrial fibrillation with a high degree of A-V block was observed.

2. The electrocardiographic response to Valsalva's maneuver was studied in these three cases and in 20 control subjects. T wave changes, sinus arrest, and nodal rhythm occurred in our patients but not in the control series.

3. It is concluded that cardiac standstill and subsequent arrhythmia in phase IV of Valsalva's maneuver is a cause of syncope following micturition and possibly in other conditions associated with Valsalva's maneuver. Its mediation through the secretion of acetylcholine in phase IV of the maneuver has been discussed.

Acknowledgment

We are indebted to Drs. Robert Friedenberg and Thomas Gibbons, and to Col. Wilbur W. Heihle, (MC) USA, for their careful criticism and useful comments. We wish also to thank Mrs. Merlene Meek and Mrs. Naomi Annin for their technical assistance.

Summario in Interlingua

Le occurrentia de collapso cardiovascular con un fortiate expiration contra le claudite glotta (manovra de Valsalva) es cognoscite depost ancian tempores. Syncope associate con le uso del bassino de lecte, con tusse, e con miction e le recente descriptiones physiologic del manovra de Valsalva ha re-sublineate le importantia clinic de effortio. In le conception traditional, le collapso cardiovascular occurre al culmine del effortio quando le rendimento cardiac es diminuite a grados critic.

Nos ha observate tres casos de syncope associate con miction in normal masculos adulte. In omne iste casos, le syncope occurreva immediatemente post le acto del miction, quando le effortio esseva completate.

Le prime caso esseva illo de un masculo de 19 annos de etate. Ille esseva observate in medio del episodio syncopal in choc con fibrillation atrial, un alte grado

de bloco atrio-ventricular, prematur pulsos ventricular, e un frequentia cardiac de 50. Iste anormalitates reverteva spontaneemente al norma. Studios additional revelava arresto sinusal, rhythmo nodal, e alterationes del vector T in le phase IV del manovra de Valsalva. Iste anormalitates esseva supprimite per atropina.

In le secunde caso le patiente collabeva post le effortio del miction. Un electrocardiogramma obtenite plure horas plus tarde revelava alterationes de unda T del typo associate con defecto myocardial postero-lateral. Iste alterationes reverteva tosto al norma. Illos non recurreva in le test de exercitio a duo grados sed appareva in phase IV del manovra de Valsalva in concomitantia con arresto sinusal e un rhythmo nodal.

Le patiente del tertie caso etiam collabeva post le effortio del miction. Arresto sinusal e rhythmo nodal occurreva in phase IV del manovra de Valsalva.

Le arresto sinusal, le rhythmo nodal, e le alterationes de unda T observate in nostre tres patientes in phase IV del manovra de Valsalva non occurreva in nostre serie de controlo o in le series de controlo de altere autores reportate in le litteratura.

Es presentate datos in supporto del these que le syncope associate con miction (e con altere situationes clinic a tension e effortio) es le resultato de un excessive secretion de acetylcholina in phase IV del manovra de Valsalva. Iste excesso de acetylcholina causa arresto cardiac e subsequente arrhythmias in un corde que ha essite sensibilisate per le reducite fluxo de sanguine coronari in phase II del manovra.

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CLINICAL IMPLICATIONS OF AN EXTENSIVE ACTUARIAL STUDY OF BUILD AND BLOOD PRESSURE*

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WHEN data derived from exceedingly large numbers of medical examinations made in connection with applications for life insurance are studied statistically to relate them to mortality experience, the results obviously will be used as the basis upon which future insurance will be underwritten. The results should also be of some interest to those concerned with conservation of life and health. For nearly 50 years studies have been carried out using data pooled from several insurance companies. The most recent of these studies [1] represents a detailed evaluation of variations in build and blood pressure in relation to mortality experience.

The purpose of this paper is to emphasize some of the highlights of that study. The investigation was designed to cover the mortality experience with ordinary insurance issued between 1935 and 1953. These policies were traced to their anniversary dates in 1954. In that portion of the investigation concerned with build nearly five million policies were studied, of which 133,000 policies had been terminated by death. In the study concerned with blood pressure, data were submitted on nearly four million policies; of these, 102,000 had been terminated by death. Because information was available regarding causes of death, it was possible to study variations in build and blood pressure not only in relation to mortality rate but also in relation to cause of death. A new basic mortality table was prepared on both men and women, medically examined, insured under standard ordinary issues during this same period of 1935 to 1953. These mortality rates, arranged by five-year age groups, form the base lines with which mortality experience in the study itself is compared. To provide a base line for analysis of causes of death, tables were prepared separately for men and for women showing standard distributions of total deaths by major cause groups, 10-year age groups at time of issue, and by duration since issue. For example, those individuals aged 40 to 45 years at the time their insurance policies were issued demonstrated an average mortality rate during the first five policy years of 2.54 deaths per thousand per year. During the next five years this mortality rate had increased to 5.34 deaths per thousand per year. This represents deaths from all causes (other than

* Received for publication April 29, 1960.

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Presented at the Clinical Session of the Forty-first Annual Meeting of The American College of Physicians, San Francisco, California, April 5, 1960.

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war deaths) and it is a mortality rate anticipated when presumably "normal," "healthy" individuals are insured at standard insurance premiums. To continue the example, the distribution table of deaths by cause would indicate that of the 2.54 deaths per thousand per year, in the group above, 43.4% of the men and 13.3% of the women died of diseases of the heart and circulatory system. During the second quinquennial duration, when the rate is 5.34 deaths per thousand per year, diseases of the heart and circulatory system caused 49.4% of the male deaths and 18.2% of the deaths among women. It is with comparable base lines of mortality rate and with distribution of death by cause that the many subdivisions of build and blood pressure have been compared.

The average height and weight as determined in this study has not changed with any striking consistency when compared to averages derived in the first intercompany study nearly 50 years ago. In general, the average heights for males under 30 and for women of all age groups are a little higher than were shown in the previous study of 1912. Men today are slightly heavier, but women average a few pounds lighter than did people of similar sex and age groups prior to World War I. Among the insured persons, 20% of the men and 23% of the women weighed 10% or more than the average; 6% of the men and 11% of the women weighed 20% or more than average weight.

Not part of this intercompany project but done independently by one company was an ancillary study of weight ranges associated with the lowest mortality rate.[2] Consistently it was found that in males over 30 and in females over 20 years of age the "ideal" weight, or that weight associated with the lowest mortality experience, was lower than the "average weight."

Overweight, generally, had to exceed 25% above average weight before appreciable increases in mortality rate were demonstrated. With increasing policy duration the mortality rate improves for underweights and for those individuals with average or near average weights. Moderate degrees of overweight (20 to 25% above average) are associated with some increase in mortality rate in later durations, but marked overweight (30% or more in excess of average) is associated with a sharp upward trend in mortality—in some instances exceeding twice the expected rate.

When the distribution of death by cause among the overweight groups is compared to the general distribution tables, it is clear that deaths due to degenerative diseases of the cardiovascular system are considerably increased in number. In some overweight groups the incidence of fatal heart disease is doubled, the incidence of vascular lesions of the central nervous system is significantly increased, that of deaths from intrinsic renal disease is two and one-half times the expected, and that of deaths attributed to diabetes is increased three and one-half times.

An interesting and encouraging special study was carried out on people who had at one time been sufficiently overweight to merit substandard in-

TABLE 1A

Average Weights for Men and Women According to Height and Age

Height (in Shoes)	Weight in Pounds (in Indoor Clothing)							
	Ages 15–16	Ages 17–19	Ages 20–24	Ages 25–29	Ages 30–39	Ages 40–49	Ages 50–59	Ages 60–69
	Men							
5′0″	98	113	122	128	131	134	136	133
1″	102	116	125	131	134	137	139	136
2″	107	119	128	134	137	140	142	139
3″	112	123	132	138	141	144	145	142
4″	117	127	136	141	145	148	149	146
5″	122	131	139	144	149	152	153	150
6″	127	135	142	148	153	156	157	154
7″	132	139	145	151	157	161	162	159
8″	137	143	149	155	161	165	166	163
9″	142	147	153	159	165	169	170	168
10″	146	151	157	163	170	174	175	173
11″	150	155	161	167	174	178	180	178
6′0″	154	160	166	172	179	183	185	183
1″	159	164	170	177	183	187	189	188
2″	164	168	174	182	188	192	194	193
3″	169	172	178	186	193	197	199	198
4″	*	176	181	190	199	203	205	204

* Average weights not determined because of insufficient data. Source: Build and Blood Pressure Study, 1959, Society of Actuaries.

TABLE 1B

Average Weights for Men and Women According to Height and Age

Height (in Shoes)	Weight in Pounds (in Indoor Clothing)							
	Ages 15–16	Ages 17–19	Ages 20–24	Ages 25–29	Ages 30–39	Ages 40–49	Ages 50–59	Ages 60–69
	Women							
4′10″	97	99	102	107	115	122	125	127
11″	100	102	105	110	117	124	127	129
5′0″	103	105	108	113	120	127	130	131
1″	107	109	112	116	123	130	133	134
2″	111	113	115	119	126	133	136	137
3″	114	116	118	122	129	136	140	141
4″	117	120	121	125	132	140	144	145
5″	121	124	125	129	135	143	148	149
6″	125	127	129	133	139	147	152	153
7″	128	130	132	136	142	151	156	157
8″	132	134	136	140	146	155	160	161
9″	136	138	140	144	150	159	164	165
10″	*	142	144	148	154	164	169	*
11″	*	147	149	153	159	169	174	*
6′0″	*	152	154	158	164	174	180	*

* Average weights not determined because of insufficient data. Source: Build and Blood Pressure Study, 1959, Society of Actuaries.

TABLE 2A*

Desirable Weights for Men and Women According to Height and Frame.
Ages 25 and Over

Height (in Shoes)	Weight in Pounds (in Indoor Clothing)		
	Small Frame	Medium Frame	Large Frame
	Men		
5′2″	112–120	118–129	126–141
3″	115–123	121–133	129–144
4″	118–126	124–136	132–148
5″	121–129	127–139	135–152
6″	124–133	130–143	138–156
7″	128–137	134–147	142–161
8″	132–141	138–152	147–166
9″	136–145	142–156	151–170
10″	140–150	146–160	155–174
11″	144–154	150–165	159–179
6′0″	148–158	154–170	164–184
1″	152–162	158–175	168–189
2″	156–167	162–180	173–194
3″	160–171	167–185	178–199
4″	164–175	172–190	182–204

* Prepared by the Metropolitan Life Insurance Company. Derived primarily from data of the Build and Blood Pressure Study, 1959, Society of Actuaries.

TABLE 2B*

Desirable Weights for Men and Women According to Height and Frame.
Ages 25 and Over

Height (in Shoes)	Weight in Pounds (in Indoor Clothing)		
	Small Frame	Medium Frame	Large Frame
	Women		
4′10″	92–98	96–107	104–119
11″	94–101	98–110	106–122
5′0″	96–104	101–113	109–125
1″	99–107	104–116	112–128
2″	102–110	107–119	115–131
3″	105–113	110–122	118–134
4″	108–116	113–126	121–138
5″	111–119	116–130	125–142
6″	114–123	120–135	129–146
7″	118–127	124–139	133–150
8″	122–131	128–143	137–154
9″	126–135	132–147	141–158
10″	130–140	136–151	145–163
11″	134–144	140–155	149–168
6′0″	138–148	144–159	153–173

* Prepared by the Metropolitan Life Insurance Company. Derived primarily from data of the Build and Blood Pressure Study, 1959, Society of Actuaries.

surance and who later, by reason of weight reduction, were able to qualify for standard rates. (While companies vary in their weight limits for standard insurance, in general a person rated for overweight would have to have a weight exceeding 25% above average weight for sex, height, and age.) The period of time during which the weight reduction has been maintained in order to achieve premium reduction also varies from one company to another. For the most part, the lower weight must have been maintained for at least one year (although in some instances only six months' time has been required) before a premium revision is considered. Whether or not the reduced weight was maintained once the premium rate was decreased is a factor which cannot be determined from this type of study. The mortality experience among those who reduced their weight was comparable to the experience in the standard groups. These results are in accord with the findings of an earlier insurance study [8] and should offer to the clinician statistical justification and incentive for a weight reduction program.

In reporting blood pressure observations on life insurance examinations physicians demonstrate the apparent popularity of "round numbers." The distribution tables show a peaking at both systolic and diastolic levels evenly divisible by 10, and secondary peaking at those levels ending in "5." The most commonly recorded blood pressures are 120/70, 120/80, and 130/80. This may represent a disregard for accuracy but we see it with great frequency in the same reports of examiners who record height to the nearest one-half inch and weight to the nearest pound. It may represent an expression of the examiners' concept of "significant figures"—an awareness of the futility of recording with great accuracy a finding subject to so many variables.

Of paramount interest are the determinations of those levels of systolic and diastolic pressure above which an increase in mortality experience is demonstrable. One would not expect to find and definitely we did not find a single rigid dividing point applicable to all ages and to both sexes. Outstanding among the findings is the sharp increase in mortality experience associated with even minor increases in blood pressure.

With diastolic pressures in the range 83 to 87 mm. Hg, significant increases in mortality rate (more than 25% above that expected) are demonstrated in men when the systolic pressures are in the range 138 to 147 mm. Hg. This is particularly true for the age group 30 to 50 where the mortality ratio of actual to expected deaths is over 150%. The causes of death associated with this increase in mortality rate are predominantly cerebrovascular accidents and diseases of the heart, including coronary artery disease. In males under 40 with blood pressures in the range 138/83 to 147/92, fatal heart disease is more than twice as frequent, and fatal vascular lesions of the central nervous system nearly four times as frequent, as are seen in the average distribution of causes of death for males of the same age group. With blood pressures of this borderline level, it might well be anticipated that increases in mortality would be deferred for many years.

Clinically one does not ordinarily associate the likelihood of an early death with the finding of a blood pressure of 145/90 in a man of 35. The increase in mortality rate is, however, very definitely present, and it is measurable when we use the accurate base lines possible in a statistical study of this size. The actual mortality rate in men with systolic pressures in the range of 138 to 147 mm. Hg and with all diastolic pressures combined during the first five years shows a greater deviation from the expected rate than in any quinquennial period covered in this study. The ratio of actual to expected mortality during the first five years is 179%, but for periods six to 10, 11 to 15, and 16 to 19 years the ratios are 135%, 136%, and 138%. Granted that many of these early unexpected deaths are in those individuals with the higher diastolic pressures, the frequency with which diastolic pressures over 95 are associated with systolic pressures of from 138 to 147 mm. Hg is less than one per cent. I cannot explain why this excessive early mortality occurs. With higher systolic pressures the mortality rates are even higher, but the rates tend to remain more nearly the same for successive five-year periods.

Among women the extent of the increased mortality associated with increased blood pressure is much less than in males. The actual mortality rate for women who have the same levels of blood pressure which in men are associated with mortality rates twice the expected, frequently are no higher than the normal expected rates.

We are aware that the blood pressure readings recorded on life insurance examinations must always be evaluated critically. The examinations are not always done under ideal circumstances. The examining physician may be subjected to varying degrees of "pressure" by the agent or by the person proposed for insurance. The doctor may honestly believe that insurance companies are too severe in their evaluation of blood pressure elevations. This may prompt him to record only the lowest of several observations of a "labile" blood pressure. As a guide to future life insurance underwriting practices the value of the findings in this study is distinct. If there are inherent biases in the figures for blood pressures recorded on life insurance examinations, the same biases will likely prevail with similar frequency and with similar results in future insurance examinations.

Different criteria should be applied to the data in determining whether the results contain information of value to the clinician. If factors exist which have influenced the recording of blood pressure readings at significantly lower than the observed levels, the frequency distribution pattern should not be comparable to the distribution pattern of blood pressure observations in a group of people examined for reasons entirely different than the acquisition of life insurance. A study of this type is currently being carried out by one of the insurance companies. The actual size of the variations represented by or reflected in the mortality rate should constantly be kept in mind. While the variations are important guides in determining whether increases in premium rates should be charged, they are quite small

when reviewed in the light of the usual prognostic impressions of clinical material. For example, a doubled mortality expectancy at ages under 35 is in reality an expectancy of only one extra death per thousand per year, and this includes deaths from all causes. While the rate increases with age, in the group aged 65 to 69 a doubled mortality rate still represents only slightly more than 40 deaths per thousand per year.

If a physician has under his personal care for one year 100 patients aged 65 to 69 years and if during that year only four die (from all causes), he would probably classify such a group as having done rather well. Most insurance companies, however, cannot insure individuals in that age group with that expected mortality rate except at very greatly increased premiums.

It is unfortunate that many people who have received "rated" life insurance based upon physical findings consider themselves in need of treatment for the correction of their impairment. The very nature of insurance premiums makes it mandatory that increased rates be charged when blood pressures associated with increased mortality rate are found. However, I hope I have made it clear that the absolute size of some of these variations is at times so small, particularly in young people and in association with borderline blood pressures, that they should not be used as criteria for active therapy.

SUMMARIO IN INTERLINGUA

Le cifras de mortalitate e le distribution frequential del causas de morte in plure milliones subjectos sub assecurantia del vita esseva studiate extensemente in relation a variationes de statura e de tension del sanguine. Le statura medie de juvene masculos e femininas de omne gruppos de etate ha crescite levemente depost un previe studio similemente concernite con le statura circa cinquanta annos retro. Masculos es alicun libras plus pesante e femininas alicun libras minus pesante que lo que esseva demonstate pro subjectos de comparabile grandores e etates ante le prime guerra mundial. A generalmente parlar, leve augmentos del cifras de mortalitate es apparente quando le excesso del peso es plus que 25% supra le peso medie. Con excessos plus marcate del peso, il occurre un acute trend in alto in le cifras de mortalitate. Iste augmento del mortalitate reflecte predominantemente un augmentate frequentia de morbos renal cardiovascular.

Augmentos del mortalitate probabile, sufficientemente marcate pro esser importante ab le puncto de vista del subscriber polissas de assecurantia vital, es associate con tensiones de sanguine de inter 138/83 e 147/92 e con omne nivellos in supra de isto. Il existe rationes a supponer que le nivellos del tension de sanguine registrate in examines pro assecurantias vital es distorquite. Le alte cifras de mortalitate a plus juvene etates representa forsan de facto micrissime numeros. Il es a causa de iste rationes que le presente studio—que es definitemente de valor como guida in le evalutation de assecurantias vital—es restringite in su importantia ab le puncto de vista del medico in le practica clinic.

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CASE REPORTS

ACUTE GLOMERULONEPHRITIS IN AN ADULT WITH LONGSTANDING DIABETES MELLITUS *†

By Stephen E. Epstein ‡ and E. Lovell Becker, M.D., *New York, N. Y.*

Kimmelstiel and Wilson [1] in 1936 first described the nodular lesion found in the glomeruli of patients with diabetes. Their original study was based on autopsy findings and included an evaluation of the associated clinical findings. Since that time, many studies of the clinical syndrome associated with this lesion have been reported. However, percutaneous renal biopsy has made it possible to evaluate the specific relationship between the clinical signs and symptoms and the pathologic lesion studied. Since a variety of diseases can produce the same clinical manifestations, careful clinical and laboratory investigation are required to establish the correct diagnosis.

Recently a 51-year-old man with diabetes was admitted to The New York Hospital with a presumptive diagnosis of Kimmelstiel-Wilson syndrome and was subsequently found to have acute glomerulonephritis. This case illustrates an interesting problem in differential diagnosis and an unusual example of acute glomerulonephritis associated with diabetes mellitus. No similar case reports were found in reviewing the literature of the past 20 years.

Case Report

The patient was admitted to The New York Hospital with the chief complaint of swelling of the face, hands, abdomen, and ankles for the preceding two and one-half weeks. Four weeks prior to admission the patient developed a mild, nonproductive cough, sore throat, shaking chills, and a fever of 39.5° C. He received 300,000 units of crystalline procaine penicillin G from his private physician, and in 12 hours the fever abated. Approximately 12 days later, or 16 days prior to hospitalization, the patient noted the onset of anorexia, fatigue, dyspnea, and swelling of his hands, abdomen, and ankles, as well as puffiness about his face and eyes. There was a weight gain of 15 pounds; no change was observed in the color or total amount of urine excreted.

The patient had had diabetes mellitus for the past 12 years. During this time his requirement for insulin had increased until on hospitalization he was taking 80 units of protamine zinc insulin (PZI) and 40 units of crystalline zinc insulin (CZI) per day. His diabetes had been fairly well controlled, with the exception of several mild insulin reactions and an occasional mild episode of acidosis.

On physical examination the patient was obese and did not appear acutely ill. Temperature was 37° C, pulse 100, respiration 26, and blood pressure 170/90 mm. Hg.

* Received May 17, 1960.
† This work was supported in part by a grant from the New York Heart Association.
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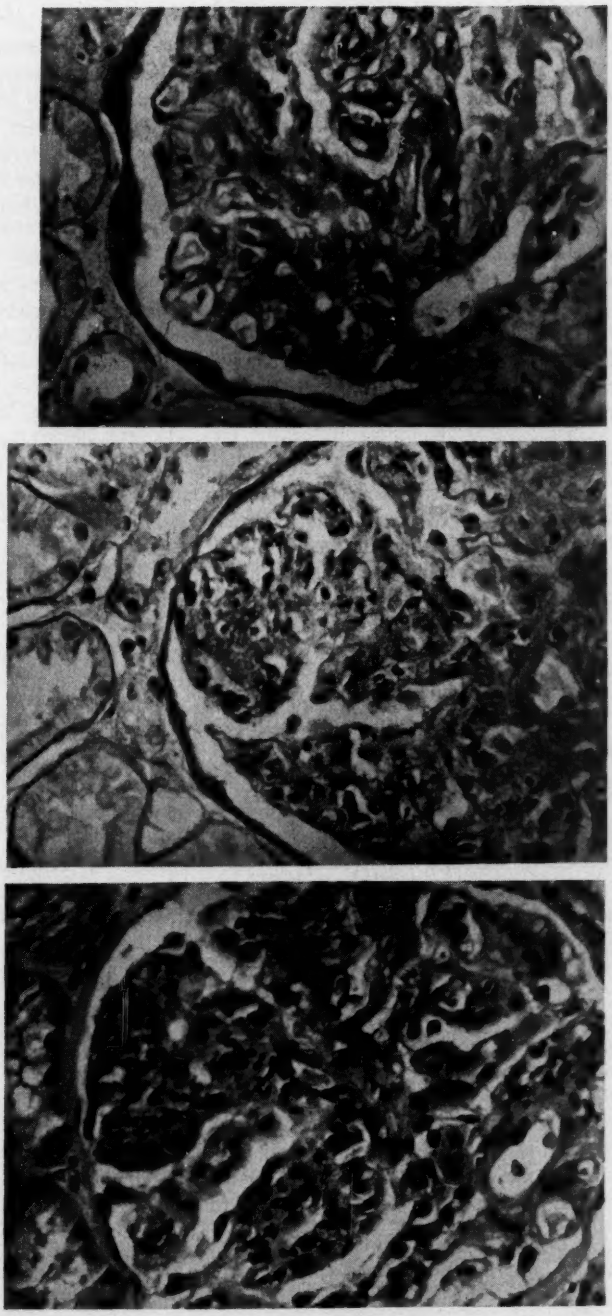
There was puffiness about the eyes, face, and hands with 3-plus pitting edema of the pretibial and sacral areas. Capillary aneurysms were observed in both optic fundi, but no other abnormalities were noted. Examination of the chest showed dullness to percussion and fine inspiratory râles in the lower one-third of both lung fields posteriorly. Cardiac dullness, by percussion, extended 11 cm. to the left of the mid-sternal line. A grade one mid-systolic, nonradiating murmur was heard along the left sternal border. A split second sound was heard both at the base and at the apex of the heart. All other physical findings were within normal limits.

Laboratory studies showed the patient's hematocrit to be 37%, hemoglobin 12.5 gm.%, red blood cell count 4.8 million, and white blood cell and differential counts normal. The urine was clear yellow, showed a specific gravity of 1.015, pH 5.0, albumin 3-plus, and no sugar or acetone. The microscopic examination revealed 5 to 10 red blood cells and 10 to 20 white blood cells per high power field with many granular and hyaline casts. The corrected erythrocyte sedimentation rate (Wintrobe) was 34 mm. per hour. Repeated urinalyses revealed persistent hematuria, pyuria, and cylindruria. The Addis counts for 12 hours revealed 350,000 casts, 23.5 million epithelial and white blood cells, and 5.5 million red blood cells. Two weeks after admission, the Addis count for 12 hours showed 800,000 casts, 95.5 million epithelial and white blood cells, and 27 million red blood cells. The specific gravity of the urine was never above 1.012, corrected for temperature and protein. The urine protein content on two determinations was 2.5 gm. and 2.6 gm. per 24 hours. The total cholesterol was 207 mg.% and the blood urea nitrogen ranged from 52 mg.% on admission to 42 mg.% at the time of discharge from the hospital. Serum albumin and globulin values were 3.4 and 2.2 gm.% and the urea clearance ranged from 20% to 32% of normal. Serum electrolytes were normal. Urine showed less than 10^3 bacteria per ml. Beta-hemolytic streptococci were cultured from the throat, and the antistreptolysin titer was 900 units. Precipitins to the M protein of types 12 and 15 streptococcus were present in the serum. Serum electrophoresis and electrocardiogram findings were normal. Chest x-rays showed moderate pulmonary vascular congestion and a slightly enlarged heart. Intravenous pyelograms with 70% Urokon revealed poorly functioning, non-hydronephrotic kidneys with poorly visualized upper urinary tracts. Calyces which were visualized were delicately cupped. The venous pressure, which was 150 mm. of saline at the sternal angle on admission to the hospital, dropped to 68 mm. of saline at the time of discharge. Circulation time by the arm to tongue method (sodium succinate) was normal.

Hospital Course: On admission the patient's blood pressure was 170/90 mm. Hg, and it remained in this range until discharge. On bed rest, a low-salt diet (3 gm. per day), digitalis, and diuretic therapy, the patient lost a total of 10.6 kilos of weight during his hospital stay. His dosage of insulin, which was 120 units on admission, was decreased, so that he was discharged from the hospital on 30 units of NPH insulin per day. During his hospitalization there was a clearing of the pulmonary congestion. Percutaneous renal biopsy was performed (Figure 1). The glomeruli showed marked increase in cells. There was some epithelial and endothelial proliferation but the majority of the cells were neutrophils. There was a tendency to hyperlobulation of the glomerular capillaries and the inflammatory cells involved single or multiple lobules of the glomerulus. In places the capillaries were adherent to Bowman's capsules, but this was not prominent. Periodic acid Schiff (PAS) stains revealed an increase in the amount of positive staining material within the walls of, or between, glomerular capillaries, but no nodular lesions were present. The afferent and efferent arterioles showed only slight sclerosis. These changes were compatible with acute glomerulonephritis, and the changes seen in PAS stains could be attributed either to very early diffuse diabetic glomerulosclerosis or to glomerulonephritis.



A B C

FIG. 1. A. Typical glomerulus showing hypercellularity and infiltration with neutrophils. B. Lobule of glomerulus showing necrosis and infiltration with neutrophils. C. Hilus of glomerulus showing diffuse thickening of the capillary wall.

Comment

The Kimmelstiel-Wilson syndrome in this patient was suggested by the 12-year history of diabetes, the generalized edema, the albuminuria, the hypertension, and the diabetic retinopathy. This diagnosis seemed reasonable, since Rogers and Robbins [2] found that 64% of patients who had had diabetes for from 10 to 14 years had the lesion of nodular intercapillary glomerular sclerosis at autopsy. Others have reported that among patients with the nodular lesion about 60% had hypertension, 66% had albuminuria, and 86 to 100% had diabetic retinopathy.[3, 4]

The difficulty encountered in making this diagnosis is apparent, since Kimmelstiel-Wilson disease is a pathologic diagnosis based on the presence of typical nodular lesions in the glomeruli.[1] Subsequent to the original description, an attempt was made to define a clinical syndrome associated with the renal lesion. Kimmelstiel and Porter [3] state that the diagnosis can be made with virtually 100% accuracy in a patient 50 or more years of age with chronic diabetes, nephrotic edema, albumin in the urine, and a high blood cholesterol. These authors were well aware of the difficulties in making the diagnosis clinically, since they point out that less than 10% of patients with the Kimmelstiel-Wilson lesion have a nephrotic type of edema. However, many other causes of the nephrotic syndrome [5] may produce a similar clinical picture. Rifkin et al.,[6] using the more rigid criteria of long-standing diabetes, age over 50 years, hypertension, edema, diabetic and hypertensive retinopathy, albuminuria, and fat bodies in the urine diagnosed 22 cases clinically and predicted the Kimmelstiel-Wilson lesion would be found at autopsy, which was true in all but one case. By observing such rigid criteria, many early cases of the syndrome could be overlooked. However, as soon as the diagnostic requirements are made less rigid, a much higher diagnostic error results. Rogers and Robbins [2] required only diabetes, albuminuria, edema, and hypertension for a diagnosis of Kimmelstiel-Wilson disease. Out of 41 cases diagnosed clinically using these criteria, only 28 had the Kimmelsteil-Wilson nodular lesion at autopsy. Moreover, even with their less rigid criteria, 58% of patients who were demonstrated to have the lesion on autopsy had not been assigned the diagnosis clinically.

The significance of diabetic retinopathy in the diagnosis of Kimmelstiel-Wilson lesion is of interest. Friedenwald [4] states that of a total of 55 patients with retinal capillary aneurysms, 32 showed the Kimmelstiel-Wilson kidney lesion on autopsy. Of 33 diabetic patients without capillary aneurysms, none showed the Kimmelstiel-Wilson lesion on autopsy. The author's interpretation was that the retinal lesion precedes the renal lesion. From this it seems that a diagnosis of the Kimmelstiel-Wilson lesion would be most tenuous in the absence of the retinal lesion, while the presence of the retinal lesion cannot be regarded as certain indication that the renal lesion is present.

Recently, the causative role of the nodular lesion in the pathogenesis of the clinical syndrome has been refuted by Gellman et al.[7] These authors describe a diffuse thickening of the basement membrane as being independent of and preceding the appearance of the nodular lesion. Moreover, they believe that this diffuse thickening is morphologically just as specific for diabetes as is the nodular lesion. They also statistically correlated the severity of hypertension, proteinuria, renal failure, the incidence of edema, and the presence of nephrotic syndrome

with the severity of diffuse diabetic glomerulosclerosis. This correlation was demonstrated not to be true of the nodular lesion. The authors emphasized that Kimmelstiel-Wilson disease is a pathologic diagnosis based on the presence of nodular lesions in the glomeruli, and that the clinical manifestations of diabetic nephropathy may be present without the nodular lesion. This is of particular interest in relation to the renal biopsy findings of the patient described here. In the absence of glomerular nodular lesions, Kimmelstiel-Wilson disease could not be diagnosed; however, the presence of diffuse thickening of the basement membrane was consistent with, although not pathognomonic of, diabetic glomerulosclerosis. Patients with this pathologic picture may have clinically demonstrable nephrotic edema.[7] It was thus important in the differential diagnosis to determine if the edema in our patient had a nephrotic basis.

The nephrotic syndrome has been defined as being characterized by massive edema, proteinuria, hypoproteinemia, and elevation of the serum cholesterol and lipids.[8] Schreiner,[9] however, has shown that patients having a proteinuria of greater than 3.5 gm. per day with doubly refractile bodies in the urine and without hypercholesterolemia and hypoalbuminemia have the same renal lesions on biopsy as those patients showing all the elements of the nephrotic syndrome. These patients manifest only a variable tendency to edema, hypoproteinemia, and hyperlipemia, all probably related to the duration and amount of protein loss.

In the patient cited here, the laboratory results did not satisfy any of the definitions of the nephrotic syndrome. Thus the generalized edema present in this man cannot be explained as being part of the nephrotic syndrome secondary to diabetic nephropathy. This led to the consideration that the generalized edema might be on a nephritic basis. The first evidence of nephritis was the persistent microscopic hematuria found on repeated urinalysis. Kimmelstiel and Porter [3] state that in a suspected case of intercapillary glomerulosclerosis, glomerulonephritis can be ruled out by Addis counts, for in glomerulonephritis red blood cells will appear in pathologic numbers in contrast to the lack of significant hematuria found in intercapillary glomerulosclerosis. In a series of 44 patients with uncomplicated diabetic glomerulosclerosis, Rifkin [6] found that 58% had no red blood cells per high power field, while the remaining 42% had no more than 1 to 5 red blood cells per high power field. Conversely, Ellis [10] and Fishberg [11] reported that virtually 100% of patients with acute glomerulonephritis have demonstrable hematuria.

In this patient, the history of an upper respiratory infection, with sore throat and fever which responded to penicillin therapy, was suggestive of a streptococcal infection. Laboratory confirmation was provided by the isolation of beta-hemolytic streptococcus from the throat, elevated antistreptolysin O titer, and the presence in the serum of precipitins to the M protein of type 12 streptococcus. Rammelkamp [12] and Stetson et al.[13] have shown that acute glomerulonephritis occurs in 12% of untreated patients convalescing from type 12 streptococcal pharyngitis and in 4.5% of patients receiving early penicillin therapy. The latent period of 12 days from the onset of the upper respiratory infection to the appearance of edema is consistent with the natural course of acute glomerulonephritis.

Hypertension and cardiac complications are also frequent features of acute glomerulonephritis. Usually the hypertension is moderate in degree, the most common blood pressure readings in adults being between 130 and 170 mm.

Hg systolic and below 120 mm. Hg diastolic.[11] There is much controversy regarding the nature of the cardiac condition. Patients with acute glomerulonephritis frequently show an enlarged heart, pulmonary congestion with basilar râles, and an increased venous pressure. A split second sound which can be heard out to the apex in the absence of a grossly enlarged right ventricle is suggestive of pulmonary hypertension.[14] All of these are usually considered to be classical signs of congestive heart failure, which, indeed, some authors believe is the cause of the edema of nephritis.[15] Most investigators, however, indict the kidney as the primary cause. A decreased glomerular filtration rate is believed to lead to an increased resorption of salt and water, which leads to increased venous, cardiac, and pulmonary pressures and to edema formation.[16, 17] Increased capillary permeability may play some role in the pathogenesis of edema but this is still an unsettled question.[11, 17]

The normal circulation time and normal cardiac output found in most cases of acute glomerulonephritis is used to substantiate the theory that this is an example of noncardiac circulatory congestion.[16-18] Fishberg,[11] on the other hand, believes that once dyspnea, pulmonary edema, and increased venous pressure appear, cardiac edema has complicated an original nephritic edema.

Although it is uncommon for acute glomerulonephritis to appear in a 51-year-old man,[10] the condition is by no means rare.[19] This patient's illness probably was not an exacerbation of chronic glomerulonephritis, since there was no previous history of edema, periorbital swelling or proteinuria, and no hypertensive or sclerotic retinal changes. The latent period from the upper respiratory infection to the onset of symptoms of nephritis was longer than the usual three to four days seen in chronic glomerulonephritis.[10, 11, 17, 20, 21] Further, the renal biopsy showed no evidence of chronic glomerulonephritis. The prognosis of acute glomerulonephritis in adults is poor as compared to that for the disease in children.

Only about 50% of adults with acute glomerulonephritis recover completely.[11] In a series of 32 adults with acute glomerulonephritis Earle [19] found that one-half went on to healing and the other half ran a chronic course. He found the gravest prognosis in those patients with edema, hypertension, and nitrogen retention. Hematuria and proteinuria were of little aid in determining the prognosis.

Summary

A 51-year-old-man with a 12-year history of diabetes, presenting with generalized edema, was suspected of having Kimmelstiel-Wilson disease. The difficulties inherent in making such a diagnosis are discussed, particularly in reference to the correlation between the clinical signs and symptoms and the renal pathology. Evaluation and correlation of the clinical picture, laboratory data, and renal biopsy led to the final diagnosis of acute glomerulonephritis.

Acknowledgment

The authors are indebted to Dr. John T. Ellis of the Department of Pathology and to Dr. Paul Kimmelstiel for the interpretation of the renal biopsy.

Summario in Interlingua

Un masculo de 51 annos de etate con un anamnese de 12 annos de diabete mellite se presentava con edema generalisate e esseva considerate como suspecte de morbo

de Kimmelstiel-Wilson. Le difficultates inherente in le establimento de un tal diagnose es discutite. Es etiam discutite le signification de lesiones glomerular nodular, de retinopathia diabetic, de albuminuria, e del formation de edema in diabeticos. Studios subsequente in le presente caso supportava le diagnose de glomerulonephritis acute como entitate responsabile pro le signos e symptomas incontrate. Iste diagnose esseva basate super biopsia renal, positivitate de culturas ab le gurgite pro streptococcos hemolytic beta, elevate titros de antistreptolysina-O, le demonstration de anticorpore anti streptococco typo 12, constatationes in le urina, datos del anamnese, e le examine physic. Durante que le occurrentia de glomerulonephritis acute in un masculo de 51 annos de etate es pauco commun, illo non es rar. Tamen, le association de diabete mellite de longe duration con glomerulonephritis es inusualissime, ben que il existe nulle ration proque iste duo entitates non pote occurrer in le mesme patiente.

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DIFFUSE INTRASINUSOIDAL METASTATIC CANCER OF THE LIVER*

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CASES of diffuse metastatic intrasinusoidal cancer of the liver are unique in both clinical and morphologic aspects. The clinical features include a silent and often substantial interval between the primary illness and the detection of metastasis, as well as an unusually rapid terminal course. The clinical diagnosis is often obscure, and the laboratory procedure most likely to establish the correct diagnosis has frequently not been used. The morphologic findings include an unusual distribution of metastases and an unusual location of the tumor cells within the tissues involved. In addition, the morphologic and clinical features indicate an uncommon tumor-host relationship, and suggest that an alteration on the part of the host may be responsible for the remarkable pattern of metastatic deposits. This paper describes a case of diffuse intrasinusoidal metastatic disease of the liver, and provides a review of the reported examples of this condition, with emphasis on certain unique clinical and morphologic features.

CASE REPORT

The patient was a 44-year-old female who, four months prior to the present hospital admission, had had a radical mastectomy for carcinoma of the left breast. A transfusion of whole blood was given during the operation. The surgical specimen revealed metastatic tumor in the axillary lymph nodes. Recovery from the operation was uneventful, and x-ray of the lungs did not disclose metastatic disease. Postoperative radiotherapy consisted of a total of 1,800r measured in air, directed to the anterior thoracic, the anterior and posterior axillary, and the supraclavicular ports. The total dose was given over a period of 22 days at the rate of 300r to each of two ports daily.

The patient remained well until 10 days before entering the hospital, when she noted pain over the sacral region. This was shortly followed by pain over the epigastrium, and especially over the right upper quadrant of the abdomen. The abdominal pain was progressive and severe. Nausea developed one week before hospital admission, and then vomiting occurred once or twice daily. There were also anorexia, weakness, and slight loss of weight. There had been no discoloration of the stool or change in bowel habit. The patient had not previously had gallbladder disease, and there was no known exposure to hepatotoxins or to rat-infested regions.

Physical examination revealed a dehydrated, poorly nourished woman who appeared to be seriously ill. Respiration, 26; pulse, 88; temperature, 99.4° F.; blood pressure, 130/80 mm. Hg. The skin was pallid and slightly icteric, as were the sclerae. No local recurrence of carcinoma was detected, and there was no lymphadenopathy.

The heart and lungs were negative. There were tenderness and slight rigidity over the epigastrium and right upper quadrant. Although rigidity precluded pal-

* Received for publication April 21, 1959.

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pation, the liver edge by percussion extended 5 cm. below the right costal border in the midclavicular line. The abdomen was otherwise not remarkable.

Urinalysis and hematologic examination were essentially normal. The nonprotein nitrogen was 43 mg. per 100 ml. The icterus index was 18, and the total serum bilirubin was 2.06 mg. per 100 ml., with 0.44 mg. direct-reacting. The total plasma protein was 5.70 gm. per 100 ml., with 2.80 gm. of albumin and 2.90 gm. of globulin. The prothrombin content was 30% (patient, 18.9 seconds; control, 12.7 seconds). The thymol turbidity was 2.2 units, and the serum alkaline phosphatase was 6.92 Bodansky units. Death occurred on the third hospital day. The clinical diagnosis was acute homologous serum hepatitis.

FIG. 1. The superior surface of the liver, showing broad, sharply demarcated foci of metastatic tumor.

The pathologic diagnoses were diffuse intrasinusoidal metastatic carcinoma of the liver, and metastatic involvement of lungs, myocardium, pancreas, spleen, one adrenal, and the hepatic, pancreatic, para-aortic, and mediastinal lymph nodes. Death was attributed to hepatic failure secondary to massive metastatic tumor cell infiltration.

At autopsy the liver weighed 1,800 gm. The contour, color, and consistency were not remarkable except for broad, firm, pale gray metastases that were sharply demarcated from the adjacent parenchyma. The largest of these occupied the lateral aspect of the left lobe and measured approximately 12 cm. in greatest dimension (Figure 1). At these sites the cut surfaces were firm, nonresilient, and pale gray. Elsewhere the lobular pattern was slighly accentuated, and the cut surfaces were light brownish red and of usual consistency (Figure 2). The gall-bladder and extrahepatic bile ducts were not remarkable. The portal and hepatic veins were patent. The esophageal mucosa was intact, and the submucosal veins were not dilated. The spleen weighed 350 gm. and the splenic vein was patent. The lymph nodes about the head of the pancreas and abdominal aorta disclosed tumor and were enlarged, firm, pale gray, and discrete. The rest of the abdominal viscera were not unusual.

The right and left lungs weighed 550 and 520 gm., respectively. The pleural surfaces over both lower lobes revealed a slightly raised, firm, pale gray linear net-

FIG. 2. The cut surface of the liver, showing accentuated lobular pattern at grossly uninvolved sites.

work that formed a branching serpiginous pattern. The pulmonary tissue was soft and crepitant, and the cut surfaces were pale red. The mediastinal lymph nodes were firm, pale gray, and slightly enlarged. No tumor was identified about the mastectomy scar, or within the left axilla or right breast.

Histologic examination of the firm, pale gray regions of the liver revealed massive replacement with tumor. At these sites all fields were composed of large tumor cells arranged in short cords and solid masses. Only occasional hepatic cells were discernible between the clusters of tumor cells. Supporting stroma was scant, and a trichrome stain revealed no increase of fibrous connective tissue. The portions of liver appearing grossly normal revealed an infiltration of tumor cells that lay in small cords and clusters within dilated sinusoids and between disrupted columns of liver

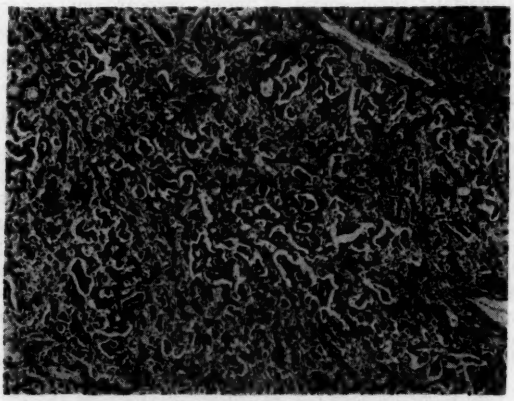

FIG. 3. Microsection of liver from portion grossly appearing uninvolved, showing intrasinusoidal tumor emboli.

cells (Figure 3). Tumor cells were also present in the periportal regions between adjacent lobules. Numerous sections from widely different portions of hepatic tissue failed to reveal a single lobule that had escaped tumor cell infiltration. Central veins and perilobular veins disclosed numerous unattached tumor emboli. No tumor cells were seen in any branch of the hepatic artery or in large branches of the portal vein. Small bile ducts were obscured by the periportal neoplastic tissue.

The lung revealed abundant tumor cell emboli in subpleural lymph spaces and in central periarterial lymph channels. Infiltration of blood vessels or alveolar air sacs was not seen. Tumor cells were also identified in the myocardium, spleen, one adrenal, and the para-aortic, pancreatic, hepatic, and mediastinal lymph nodes. Minute emboli of tumor cells were present in the periarterial lymph channels of the pancreas. The tumor cells disclosed an undifferentiated pattern throughout.

TABLE 1

Diffuse Intrasinusoidal Metastatic Cancer of the Liver

Author	Sex	Site	Type	Liver	Physical Signs	Metastases	Final Illness
1. Schuppel (1868)	M	Eye	Melanoma	7,000 gm.	Ascites	Limited, spleen	9 weeks
2. Perls (1872)	M	Lung	Carcinoma	Enlarged	Ascites		12 weeks
3. Litten (1880)	F	Pancreas	Carcinoma	6,500 gm.	Ascites, icterus	Limited	10 weeks
4. Coupland (1880)	F		Melanoma	8,200 gm.	Venous distention, icterus	Limited	2 weeks
5. Hektoen (1898)	M	Eye	Melanoma	4,100 gm.	Ascites, icterus	Limited	3 weeks
6. Hektoen (1898)	M	Eye	Melanoma	5,000 gm.	Ascites		1 week
7. LeCount (1901)	M	Eye	Melanoma	5,630 gm.	Ascites		24 weeks
8. Lilley (1911)	F	Eye	Melanoma	9,000 gm.	Ascites, icterus	Limited	28 weeks
9. French (1912)	M	Eye	Melanoma	6,400 gm.		Limited	1 week
10. Ziegler (1919)	F	Breast	Carcinoma	2,000 gm.	Icterus	Limited	4 weeks
11. Ziegler (1919)	F	Breast	Carcinoma	2,090 gm.	Ascites, icterus	Limited, marrow	
12. Sappington (1922)	F	Breast	Carcinoma	3,000 gm.	Icterus	Spleen	1 week
13. Kaufman (1929)	F	Breast				Limited	
14. Herxheimer (1930)	F	Uterus	Carcinoma	1,940 gm.		Limited	
15. Craciun (1931)	F	Breast	Carcinoma	1,220 gm.	Ascites, icterus		8 weeks
16. Muto (1935)	M	Stomach		1,740 gm.		Marrow	36 weeks
17. Oertel (1935)	M	Stomach	Carcinoma	2,240 gm.		Marrow	36 weeks
18. Isaji (1939)	M	Stomach	Carcinoma	Enlarged		Spleen, marrow	4 weeks
19. Botha (1954)	M	Skin	Melanoma	4,160 gm.		Spleen, marrow	20 weeks
20. Watson (1955)	M	Lung	Carcinoma	3,700 gm.	Icterus	Limited, spleen, marrow	2 weeks
21. Watson (1955)	M	Lung	Carcinoma	4,760 gm.	Hematemesis, icterus	Limited, spleen	2 weeks
22. Watson (1955)	M	Lung	Carcinoma	2,400 gm.		Spleen, marrow	1 week
23. Watson (1955)	M	Lung	Carcinoma	4,160 gm.			8 weeks
24. Watson (1955)	M	Lung	Carcinoma		Icterus	Limited, spleen	20 weeks
25. Micolonghi (1958)	F	Breast	Carcinoma	2,100 gm.	Ascites, hematemesis	Limited, marrow	

DISCUSSION

The sudden onset and rapid course of the illness, together with the short and asymptomatic period after treatment of the primary cancer, as well as the failure to identify recurrent tumor, were thought to indicate that the patient's hepatic disorder was not due to metastatic disease. Jaundice with right upper quadrant pain and tenderness suggested the diagnosis of ascending cholangitis. However, this was discarded in view of the absence of fever or history of previous gall-bladder disease. Because a transfusion of whole blood had been given about 120 days prior to the present illness, the diagnosis of acute homologous serum hepatitis was favored.

The literature discloses only 25 cases recorded over the last 100 years, suggesting that this type of cancer is quite uncommon. Review of these cases reveals no racial, familial or occupational predilection, although information of this kind was scarce. There were 15 males and 10 females, the difference from an equal

sex ratio apparently being due to the five cases of bronchogenic carcinoma in males reported by Watson.[18] Age was recorded in 24 cases. The youngest was 27 years and the oldest was 74 years. Thirteen were 45 or younger, 18 were 50 or younger, and the average age was 46 years. Data pertaining to these cases are listed in Table 1.

Clinical description was adequate in 23 cases. The main presenting features were referable to the biliary and gastrointestinal systems. The principal symptoms included epigastric pain, abdominal fullness, nausea, anorexia, loss of weight, and fatigue. Signs of portal vein obstruction frequently became apparent as the illness progressed, i.e., ascites in eight cases, ascites with hematemesis in one case, and distention of superficial veins over the abdomen in one case. In the case of Micolonghi et al.,[19] the clinical picture of cirrhosis was complete with jaundice, spider angiomata, dilated superficial abdominal veins, ascites, hepatosplenomegaly, bleeding esophageal varices, and hepatic coma. Jaundice thus occurred more frequently than with the common form of nodular hepatic metastasis.

A particular feature was the clinical sequence of events that followed detection of the primary cancer. In 11 cases the primary tumor was promptly followed by clinical evidence of metastatic disease. In the other 10 cases, however, a period of well-being intervened between detection of the neoplasm and the onset of symptoms due to metastatic involvement of the liver. This "silent" interval, lasting from five months to 10 years, occurred in seven patients with melanoblastoma and in three with cancer of the breast. Thus the usual clinical response to metastatic disease in the form of an inexorably progressive illness was frequently not in evidence. In both types of cases—those with and those without a temporal separation of the primary and terminal events—the clinical course of the final illness was rapid, often lasting only a few days to one month. The diagnosis was readily apparent when the signs of metastatic disease immediately followed the primary illness. However, when a period of clinical well-being, especially one of considerable duration, intervened between the primary and terminal events, the clinical diagnosis was obscure.

Autopsy was performed on all cases listed in Table 1. The sites of the primary tumor included the eye, breast, and lung, six cases each; stomach, three cases; the pancreas, uterus, and skin, one case each. In one case of melanoma[4] the primary site was not disclosed, although the clinical data indicate that the eye was the site of origin. The tumor was carcinoma in 17 cases and melanoma in the remaining eight cases. All of the carcinomas were undifferentiated except in the case of Oertel,[15] where poorly formed glands were discernible.

Pronounced enlargement of the liver without distortion of shape was the characteristic gross feature of the hepatic disorder. In addition, the color and consistency were frequently unaltered, so that the diagnosis of metastatic disease was occasionally not apparent until the microscopic sections were examined. There was one notable variation from this pattern. In the cases of Coupland,[4] Craciun et al.[13] and Micolonghi et al.,[19] the metastatic tumor cells in the liver incited a desmoplastic reaction of such degree as to warrant a diagnosis of portal cirrhosis. The authors felt that the hepatic fibrosis was a consequence of the metastatic tumor, rather than a coincidental occurrence of metastatic cancer in a pre-existing cirrhotic liver. Not the least of the reasons was that, in the latter two cases, the primary tumor was of scirrhous type. That metastatic tumor

in a pre-existing cirrhotic liver is extremely uncommon was noted by Lieber.[20]

On histologic examination the hepatic tissue revealed a diffuse distribution of tumor cells, principally within the sinusoids of the lobules, the perilobular veins, and the large branches of the portal vein. In addition, tumor cells were frequently present within the periportal zones between adjacent lobules. A characteristic feature was the loose arrangement of the unattached tumor cells that lay, singly and in minute clusters, within vascular spaces and without conspicuous tissue infiltration. In the case of Oertel,[15] no tissue invasion was identified, although the intralobular sinusoids contained abundant tumor cells, and no lobule escaped involvement. There were frequently seen compression atrophy and focal necrosis of the hepatic cord cells.

Extrahepatic involvement was widespread in 11 cases, and limited to a small number of sites in 13 cases. It included particularly the lungs, spleen, bone marrow, and lymph nodes about the porta hepatis. Involvement was characterized by a small number of minute intravascular tumor cell emboli, and bulky nodular involvement was uncommon. The massive diffuse hepatic disease, with inconspicuous, often limited, secondary deposits elsewhere, thus differs from the widespread nodular involvement that usually characterizes terminal metastatic disease. The spleen was involved more frequently than is commonly reported in metastatic disease. Willis [21] gives an over-all incidence of 4% for metastatic growths in the spleen in fatal cases of malignant disease. In the cases of intrasinusoidal cancer of the liver, eight of 23 cases disclosed splenic metastasis, an incidence of 34%. The bone marrow was not described in several cases and was presumably not examined microscopically. However, bone marrow involvement was recorded in nine of 23 cases, an incidence of 39%. Jarcho,[22] in a review of diffusely infiltrative carcinoma, found a high incidence of tumor cell emboli in the bone marrow. In addition, Weisberger and Heinle [23] have pointed out that tumor cell emboli are not infrequently found in aspiration samples of bone marrow, and they emphasize the value of this procedure in establishing the diagnosis of metastatic disease.

As pointed out by Watson,[18] the reason metastatic tumor within the liver should assume a diffuse intrasinusoidal distribution is obscure. The speculations advanced to account for such distribution include diverse portals of entry of tumor into the liver, unusually large seeding of tumor cells into the organ and, finally, an imbalance between the aggressive property of the tumor cells and the resistance of the host.

The four channels that could accommodate tumor embolization of the liver include the hepatic veins, the portal lymphatics, the hepatic artery, and the portal vein. Ziegler [9] noted emboli of cancer cells in the central veins associated with invasion of the pericentral portions of the lobules without involvement of the peripheral portions. He did not identify tumor cells within the hepatic arterioles. These observations led him to suggest that the hepatic involvement was due to a retrograde venous embolism from the right atrium through the vena cava and hepatic veins. However, no special hemodynamic alteration has been described that would provide for a massive retrograde flow of tumor cells against the vascular current, and involvement of the portal zones between adjacent lobules has been a frequent finding in other cases. As to lymphatic embolization, tumor cells entering the liver through the portal lymphatics are ordinarily released from lymph nodes about the porta hepatis. Since the lymphatic chan-

nels within the liver follow portal vessels that continually decrease in size, the resulting tumor tends to be bulky about the porta hepatis, and attenuated about the periphery of the metastatic site.[21] The tumor cells in the present case were found principally in the blood vascular spaces, rather than within lymph channels. Thus, the gross pattern and histologic distribution within the liver fail to support the suggestion that either lymphogenous dissemination or retrograde embolization through the hepatic veins is responsible for the diffuse metastatic process.

The distribution of tumor cells could be due to a selective embolization of the hepatic artery. Against this, however, is the fact that tumor cells were seldom found with the branches of the hepatic artery. Also, according to Willis,[21] dissemination of tumor from the lungs is responsible for cancer emboli entering the liver through the hepatic artery. This presupposes systemic transport of tumor cells in the arterial circuit, so that a wide distribution of extrahepatic metastases might be expected. In a substantial proportion of the recorded cases, however, extrahepatic metastasis was limited to a small number of sites. In addition, pulmonary involvement was mainly lymphangitic, the tumor cells being distributed within the subpleural and periarterial lymph channels. Also, the pulmonary metastases were consistently much less extensive than was the hepatic involvement. Therefore, it would seem unusual for the relatively slight pulmonary involvement to be the main source of the massive and diffuse hepatic disease.

The question of the portal vein as a channel remains. In the reported cases of diffuse intrasinusoidal metastasis of the liver, there is no morphologic finding that precludes this vessel as the principal route of tumor cell entrance. The site of entry, however, is not known. Perforation of a hilar lymph node into the portal vein could account for a massive influx of tumor cells into the liver, and metastatic involvement of the lymph nodes about the porta hepatis was a common finding in the reported cases. Schuppel [1] suggested this explanation, ascribing the diffuse hepatic involvement to a sudden influx of a large number of tumor cells through the portal vein. However, hepatic metastases ordinarily arise from separate emboli that proliferate and spread showers of tumor cells into small ramifications of the portal venous system. The resultant metastases tend to be discretely nodular and unevenly dispersed. This was demonstrated by Lucke et al.,[24] who found that inoculation of V2 carcinoma cells into a mesenteric branch of the portal vein in rabbits was attended by the formation of metastases that were consistently nodular. Thus there is little evidence to indicate that a peculiarity in the route of hepatic embolization is responsible for the unusual pattern of the tumor cells within that organ.

Oertel [15] suggested that a disturbance of the usual tumor-host relationship might account for the predominantly intrasinusoidal growth of tumor cells within all lobules of an entire liver. He observed that atrophy of the hepatic cord cells was often pronounced and widespread, and suggested that the tumor cells were competing with the parenchymatous cells for nutritive substances, so that the former might flourish at the expense of the latter. Most authors, however, have attributed the atrophy to direct compression by tumor cells.

In the case of Craciun et al.,[13] intensive radiotherapy was applied after mastetectomy for cancer of the breast, and these authors suggest that the radiation may have modified the behavior of the tumor. In most cases, however, radiotherapy was not applied. It is also possible that the tumor cells in these cases are extremely malignant and resistant to the restraining influence of the

host. If this hypothesis were correct, it would be expected that the neoplastic process would spread widely throughout many tissues, whereas in fact the tumor cells were massively concentrated in the liver and were sparse elsewhere. In the case of French,[8] no metastases were found outside the liver except minutely in the lymph nodes at the anterior margin of the diaphragm and about the head of the pancreas; in the case of Coupland,[4] no metastases were found outside the liver. It would thus appear unlikely that the unique distribution of tumor cells within the liver can be ascribed entirely to a biologic peculiarity of the malignant cells.

Zeidman [25] pointed out that in the metastatic process most tumor emboli succumb, and those that survive are capable of invading the vessel wall. Takahashi [26] felt that variation in the production of metastasis is not so much the failure of the neoplastic cells to make their way into the bloodstream as their inability to survive and grow after arrest in the vessels of an organ. In the cases here described, the tumor cells not only survived within the vessels, but also proliferated, as indicated by the massive vascular filling and the presence of mitotic figures. Furthermore, infiltration of the perivascular tissue was often inconspicuous. Therefore, it seems plausible on the basis of the histologic findings that the factor responsible for the unusual pattern of intravascular growth is an alteration of the restraining influence of the host. Clinical features consistent with this view include the frequency with which a significantly long period of apparent good health supervenes between the treatment of the primary cancer and the onset of the final illness. In addition, the abrupt onset and rapid progress of the final illness further suggest an alteration of the tumor-host relationship.

Summary

Review of the literature reveals 25 cases of diffuse intrasinusoidal metastatic cancer of the liver. The primary tumors have been melanomas of the eye and undifferentiated carcinomas of the breast, lung, or stomach. Clinically, a period of subjective well-being often follows treatment of the primary tumor, after which there are the onset of epigastric pain, upper abdominal fullness, and frequently jaundice with signs of portal obstruction. The onset tends to be abrupt, and the course is usually rapid. The laboratory procedure most likely to secure the correct clinical diagnosis is microscopic examination of aspirated bone marrow. The characteristic morphologic features are massive hepatic enlargement without distortion of shape, diffuse tumor cell infiltration of the liver that is principally intravascular, compression atrophy of hepatic parenchyma, and extrahepatic metastases, often of limited distribution, that affect principally the lungs, lymph nodes, spleen, and bone marrow. Reasons are provided to suggest that the unusual distribution of tumor cells may be due to an alteration of the resistance of the host to the malignant process, rather than to an unusual route of metastasis or to a biologic peculiarity of the tumor cells.

Summario in Interlingua

Es describite un caso de diffuse cancere metastatic intrasinusoidic del hepate vidite in un femina de racia blanc de 44 annos de etate. Le litteratura concernite con simile casos es revistate. Esseva trovate 25 tal casos. Le principal characteristicas clinic include un periodo de ben-esser subjective, frequentemente de longo duration,

post un apparentemente successose tractamento de cancere primari, usualmente del oculo, del mamma, del pulmon, o del stomacho. Seque alora dolores epigastric, plenitude del abdomine superior, e frequentemente jalnessa con signos de obstruction del vena portal. Le declaration ha un tendentia de esser abrupte, e le curso del morbo es usualmente rapide. Le plus utile test diagnostic es le examine microscopic de medulla ossee. Le characteristic aspectos morphologic include un massive allargamento del hepate sin distortion de su conformation, diffuse infiltration hepatic de cellulas tumoric de character principalmente intravascular, atrophia compressori del parenchyma hepatic, e metastases que affice particularmente le pulmones, le splen, le nodos lymphatic, e le medulla ossee. Le explication del diffuse distribution intravascular del tumor metastatic es obscur. Le varie explicationes possibile que ha essite proponite es un pluralitate del portas de entrata del tumor in le hepate, un massive semination de cellulas tumoric in le vena portal, e un distribution in le relation inter tumor e hospite. Un consideration detaliate de iste possibilitates indica que le factor responsabile pro le configuration inusual del crescentia intravascular es un alteration del resistentia del hospite contra le aggressive proprietates del cellulas tumoric.

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MYOTONIA DYSTROPHICA: A CASE REPORT WITH SEX CHROMATIN STUDIES *

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Myotonia dystrophica is a familial, progressive myopathy associated with degenerative changes in other tissues. These include premature baldness, colloid goiter with a low basal metabolic rate, distinctive presenile cataracts, and testicular atrophy. Eventually myotonia develops, then progressive atrophy and weakness in selected muscle groups in the face, neck, and extremities. When the trait is fully expressed in a male, the testicular pathology is remarkably similar to that described in Klinefelter's syndrome.[1, 2]

Since the discovery by Barr and his associates [3] that genetic sex can be determined by the presence or absence of a specific chromatin mass in the nuclei of various body cells, this technic has been applied to the hermaphroditic and testicular dystrophic group of diseases, with interesting results. For example, Ferguson-Smith and his associates [4] found in a series of patients with Kline-

* Received for publication May 1, 1959.
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The opinions contained herein are those of the authors and do not necessarily reflect the view of the Navy Department.
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felter's syndrome that 40% were genetically female. This implies true sex reversal during embryonic development. In myotonia dystrophica, only one case with genetic sex studies has been reported, to our knowledge.[5] In that case (a patient with the characteristic findings of Klinefelter's syndrome in whom muscular weakness, atrophy, and myotonia developed at age 28), chromatin-positive cells were found and the patient was classified as a genetic female.

It is the purpose of this report to present a case of myotonia dystrophica, hitherto undiagnosed, who is chromatin-negative, or a genetic male.

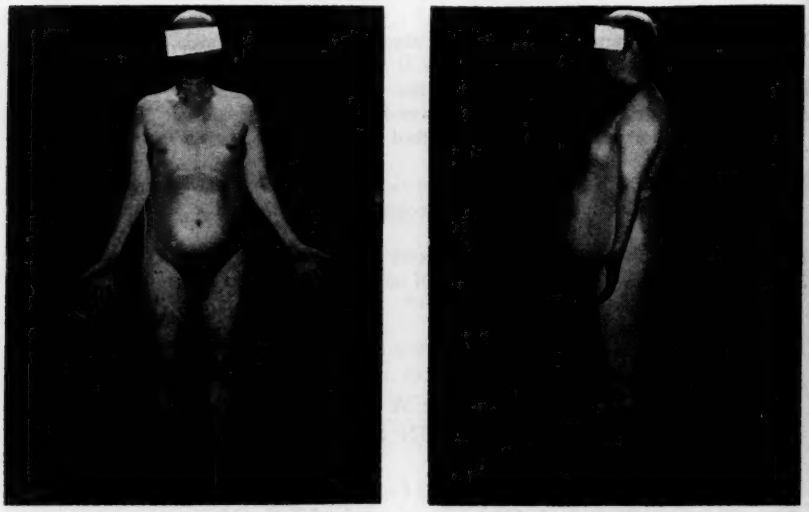

FIG. 1. Patient at age 37, front and side views. Note the atrophied neck muscles, forearms, and hypothenar spaces. The testes are small.

CASE REPORT

A 37-year-old Caucasian naval enlisted man was admitted to Portsmouth Naval Hospital on January 2, 1959, with the chief complaints of lethargy and muscular weakness.

The patient had served on continuous active duty in the U. S. Navy since October, 1942. He had begun to lose his hair at age 19, in 1940. By 1945 he was almost completely bald. In 1949 he received fractures of two toes of his left foot when he dropped a hatch cover on the foot aboard an aircraft carrier. The fractures healed uneventfully. Subsequently, the patient noted increasing fatigue, obesity, and gradual loss of libido. Because of these symptoms he was hospitalized at Portsmouth Naval Hospital in 1950. Prominent trunk obesity, a firm, diffusely enlarged thyroid gland, and atrophic testes were noted at that time. The basal metabolic rate was minus 22%. The patient was treated with desiccated thyroid, 180 mg. daily, and returned to duty. He discontinued thyroid medication after two months because "it no longer helped." Further hospitalization did not occur until September, 1953, when he sustained traumatic amputation of the distal tips of several fingers of both hands on a jointer machine. Healing was uneventful. In May, 1955, he was hospitalized at U. S. Naval Hospital, St. Albans, N. Y., at the request of his ship's

superior officers, who noted that his performance of duties had steadily deteriorated. He had been demoted, he stumbled frequently when moving about the ship, and his Chief Petty Officer recorded that he could not hit a chisel properly with a hammer nor pick up a bucket of water. Pertinent physical findings described at that time were as in 1950, with the addition of a grade III systolic murmur heard throughout the precordium. Right heart catheterization studies were therefore performed, but no abnormalities were found. Testicular biopsy and endocrine studies were also performed (Figure 3 and Table 1), and a diagnosis of Klinefelter's syndrome was made. The patient was treated with weekly testosterone propionate injections and with desiccated thyroid. This produced some subjective improvement, but he received no further therapy after being returned to duty in August, 1955. Subsequently the patient noted increasing muscular weakness in his hands, forearms, and legs. During rough seas he suffered multiple bruises from frequent falls, slips down ladders, and the dropping of hatch covers on his legs or arms. Eventually, therefore, he was re-admitted to Portsmouth Naval Hospital.

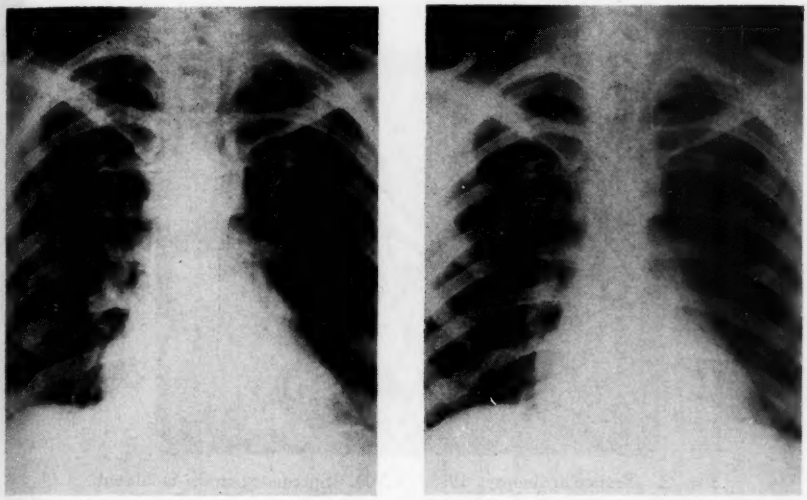

FIG. 2. Chest x-rays taken in 1955 (left) and in 1959 (right). The cardiac contour is considered to be within normal limits, and there is no significant change in the four-year interim.

Physical examination revealed a prematurely bald white male who appeared older than his chronologic age of 37 (Figure 1). Height 5′ 7″; weight, 185 pounds. Blood pressure, 110/72 mm. of Hg in both arms; blood pressure in thighs, 136/80 mm. of Hg. Pulse rate was 84 and regular. The face was expressionless, with flattening of the nasolabial folds and atrophy of the masseter and temporal muscles. The neck was small, with marked sternocleidomastoid atrophy. The thyroid gland was firm and diffusely enlarged. Obesity was prominent but localized to the abdomen, pelvic girdle, and thighs. There was evident wasting in the anterior leg compartments, but there were well developed calves. The patient walked with a slapping gait. He could not walk on his heels. There was pronounced atrophy in the forearm musculature and hypothenar eminences bilaterally. Motor weakness was present in the wrist extensors, grip-squeeze, and finger flexors bilaterally. The right deltoid

and triceps muscles were atrophied and weak. Healed amputation stumps were present on the second and fourth fingers of the right hand, and on the third and fourth fingers of the left hand. A myotonic response to percussion could be elicited only in the thenar eminences. The testes were soft and atrophic, and measured 1.5 cm. in diameter; the prostate gland was atrophic. Pubic and axillary hair was abundant; the beard was masculine. Tendon and superficial reflexes were 1-plus active, brisk and uniform. No tremors, sensory impairment, or cerebellar deficiencies could be detected. The heart was not clinically enlarged; a grade III systolic blowing murmur could be heard over the entire precordium, radiating to the left axilla and into the back. Chest x-ray was interpreted as normal, and showed no change since films taken in 1955 (Figure 2). Slit lamp examination of the eyes revealed punctate and cuneiform cataract opacities distributed throughout the anterior and posterior portions of both lenses. Hemogram, urinalysis, electrocardiogram, and skull x-rays

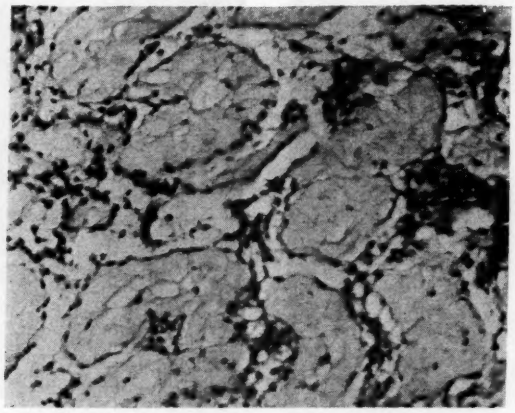

FIG. 3. Testicular biopsy, 1955. × 200. Spermatogenesis is absent.

were normal. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was negative. Sulkowitch's test was 2-plus. PPD tuberculin skin test (second strength) was 2-plus. Psychologic studies, including the Goldstein Scheerer-Weigl test, the Wechsler Adult Intelligence Scale, Bender-Gestalt, and Draw-A-Person test revealed a score in the upper level of average range, with a WAIS scale I.Q. of 106.* Endocrine data are shown in Table 1.

Methods for Sex-Chromatin Studies: Peripheral blood smears were obtained from a finger puncture and stained with Wright's stain. The slides were then sent to Dr. Donald K. Briggs, New York University-Bellevue Center, for chromatin sex analysis by the method of Davidson and Smith.[6, 7, 8]

A skin biopsy was fixed in Davidson's solution, as described by the method of Barr,[9] and processed in the routine fashion. With the use of Barr's criteria,[9] the slides were studied for sex-chromatin bodies by Dr. F. C. Holland, Jr., of the Pathology Department, Portsmouth Naval Hospital.

Results: Both skin cells and neutrophils were reported as chromatin-negative, thus implying that the genetic sex was male.

* Kindly performed by Commander Aimee W. Marrs, MSC, USNR, Clinical Psychologist, U. S. Naval Hospital, Portsmouth, Virginia.

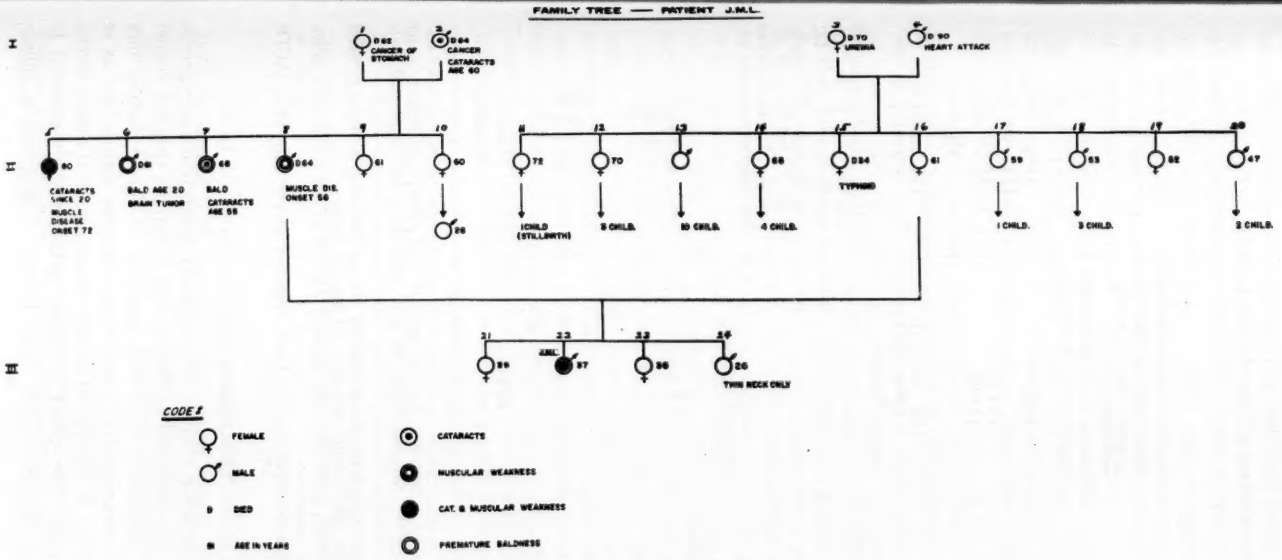

FIG. 4. Description of family "L".

Generation I: All born in United States of America; all of British ancestry.
2. Had cataracts beginning age 60.

Generation II:
5. An 80-year-old spinster who has had cataracts since age 20 and muscular weakness since age 72.
6. Prematurely bald, beginning age 20. He died of a brain tumor at age 61.
Also prematurely bald, this man has had cataracts since age 55.
7. Father of patient. Prematurely bald, he died age 64 with a muscular disease producing increasing weakness, beginning at
8. age 50. His photographs reveal a small neck and the suggestion of a myopathic facies.
9 & 10. Apparently normal. One normal child.

Generation III:
21 & 23. Sisters of patient, apparently normal.
22. Patient reported.
24. No testicular atrophy, muscular weakness or myotonia. However, he has a small neck and a diffusely enlarged thyroid gland.

TABLE 1

Combined Endocrine Data—Patient J. M. L.

Gland	Studies	1955	1959
Gonadal	Testicular biopsy	Atrophic tubules, Sertoli cells decreased, spermatogenesis absent, Leydig cells normal	
	FSH titer	Positive at 13-52-104-208 mouse units/24 hours	
Thyroid	BMR	−34%	−15%
	Serum cholesterol		118 mg.%
	24 hour I^{131} uptake	15.1%	17.4%
	After RSH	42.9%	
	Serum PBI		3.9%
Adrenal	Serum sodium	146 mEq./L.	149 mEq./L.
	Serum potassium	5.9 mEq./L.	5.9 mEq./L.
	Water tolerance	Normal	
	Oral glucose tolerance test		Fasting blood sugar 90 mg.%., at ½ hr. 136 mg.%, at 1 hr. 112 mg.%, 2 hr. 97 mg.%, 3 hr. 87 mg.%, 4 hr. 87 mg.%. Urines negative for reducing substances.
	Thorn test	Eosinophil fall 87%	
	17-Ketosteroid 24 hr. urinary excretion		
	Before ACTH	10.5 mg.	8.71 mg.
	After ACTH	16.0 mg.	9.24 mg.
	17-Hydroxycorticosteroids		22.84 mg.
Parathyroid	Serum calcium		12.2 mg.%
	Serum phosphorus		3.7 mg.%
	Alkaline phosphatase		1.3 B.U.
Other	Skull x-ray	Normal	Normal
	Spine x-rays		Normal

Urinary 17-ketosteroids were determined by the method of Callow,[17] modified by the method of Engstrom and Mason.[18] Normal values in this laboratory for adult males are 10 to 22 mg./24 hours.

Urinary 17-hydroxycorticosteroids were determined by the method of Reddy, as modified by Brown.[19] Normal values for adult males are 4 to 10 mg./24 hours.

The Thorn test was performed, using 25 units aqueous ACTH in 500 ml. normal saline, given intravenously over eight hours.

Note: The elevated 17-hydroxycorticosteroid level reported above was after ACTH stimulation.

DISCUSSION

That the multiple degenerative changes in myotonia dystrophica are genetic in origin has been readily demonstrated by Ravin and Waring's detailed studies in 13 cases from several families.[10, 11] From analysis of the pedigrees they reasoned that the disease is controlled by a single mutant gene transmitted as an atypical Mendelian dominant. It is atypical in that transmission through several generations is required before the effect becomes sufficiently pronounced to produce the characteristic disease. This was termed "progressive inheri-

tance." [10] In terms of enzyme function, this theory suggests that the mutant gene produces loss of a specific enzymatic activity. For several generations this is offset by enzymatic activity of its allelomorph, a normal gene. Eventually, however, the loss becomes so extreme that the combined activity of the normal and mutant genes is insufficient for normal function, and various degenerative changes appear. Figure 4 depicts the family tree of our patient, and evidence of "progressive inheritance" is quite apparent.

The testicular biopsy findings and endocrine data are essentially similar to those in previously reported cases of myotonia dystrophica.[12-14] The testicular abnormality represents a primary dysgenesis affecting the seminiferous tubules, with absent spermatogenesis, diminished Sertoli's cells, and intact Leydig's cells (Figure 3).

Although there have been attempts to differentiate the testicular pathology in myotonia dystrophica from that of Klinefelter's syndrome,[12, 15] it is more logical to avoid such distinctions, and to incorporate both into the broad group of basic gonadal disorders of genetic origin. Grumbach et al. have introduced the term "seminiferous tubule dysgenesis" [5] to encompass all cases of genetic malfunction leading to embryonic testes and possible sex reversal. The cause may be a single gene defect in a sex-determining gene. It should be recalled that, in normal embryology, the male determining factor (M-gene) is carried in an autosome, the female determining gene (F-gene) being carried in the X-chromosome. Normally, the combination X-X overrides the male factor, allowing female gonadal and secondary characteristics to develop. Conversely, the single X of an X-Y combination is not sufficient to override the M-gene, and a male results. In seminiferous tubule dysgenesis, the genetic defect may represent a mutant M-gene which is not suppressed by an X-X combination, and therefore a disordered, or "reinforced," [16] gonadal medulla arises, producing sex reversal. However, this would not explain those cases of Klinefelter's syndrome and our one case of myotonia dystrophica who are genetic males. Rather, in keeping with the majority of evidence correlating gene mutation with loss of a specific enzymatic activity, we like the postulate of Segal and Nelson [16] that the mutant gene affects the primordial germ cells. These cells originate in the endoderm and in about the fifth embryo week migrate to the germinal epithelium lining the genital ridge. In the absence of these primordial germ cells, the gonadal cortex regresses, and sterile gonads which resemble testes are formed, regardless of genetic sex.[5] Thus the chromatin sex of a male patient with myotonia dystrophica associated with testicular dysgenesis may be either female or male.

Summary

A case of myotonia dystrophica with testicular dysgenesis has been presented. With the use of both the peripheral smear technic of Davidson and Smith, and the skin biopsy technic of Barr, it was concluded that the patient was chromatin-negative, or a genetic male. The genetic implications are discussed.

Acknowledgment

Acknowledgment is gratefully given to Dr. Donald K. Briggs, New York University-Bellevue Medical Center, who performed the sex-chromatin studies on the peripheral blood smears of our patient.

SUMMARIO IN INTERLINGUA

Myotonia dystrophic es un myopathia familial e progressive associate con alterationes degenerative in altere tissus. Istos include calvitate prematur, struma colloidic, distinctive cataractas presenil, e atrophia testicular. In le curso del tempore, myotonia e progressive atrophia muscular se disveloppa in selegite gruppos de musculos del facie, collo, e extremitates. Quando iste character es plenmente exprimite in un masculo, le pathologia testicular es remarcabilemente simile a illo describite pro le syndrome de Klinefelter. In recente annos, studios que determina le ver sexo genetic de individuos con dystrophic disordines testicular ha essite reportate con resultatos interessante. In un serie de masculos reportate in le litteratura como casos de syndrome de Klinefelter, 40% esseva identificate como geneticamente feminin. Isto indica un disordine genetic que pote producer un reversion del sexo durante le disveloppamento embryonic. Secundo nostre informationes, non plus que un sol caso de myotonia dystrophic con studios de sexo genetic ha essite publicate (Grumbach, Blanc, e Engel). In ille caso le patiente esseva classificate como geneticamente feminin, de novo—apparentemente—un indication de reversion del sexo.

In le presente reporto nos describe le caso de un altere patiente con le constatationes characteristic de myotonia dystrophic, incluse dysgenese testicular, in qui le examine de tissu cutanee e de frottis de sanguine peripheric esseva negative quanto al presentia de corpores nucleari de chromatina sexual, de maniera que ille debeva esser classificate como de sexo mascule.

Il pare, per consequente, que—in le syndromes a dysgenese testicular (1) de Klinefelter e (2) de myotonia dystrophic—le sexo genetic pote esser mascule si ben como feminin. Le causa de un tal disordine gonadal es possibilemente un sol defecto genic, resultante in non-disveloppate testes embryonic, sin reguardo al combination del chromosomas de sexo. Nos trova bon le postulato de Segal e Nelson que le mutante gen affice probabilemente le cellulas germinal primordial in le embryo durante le prime phases de su disveloppamento. Iste cellulas ha lor origine in le endodermo, e durante circa le quinte septimana embryonal illos migra verso le epithelio germinal que revesti le cresta genital. In le absentia de functionante cellulas germinal primordial, le cortice gonadal regrede, e sterile gonades de apparentia simile a testes es formate. Per consequente, le sexo chromatinic de un patiente con myotonia dystrophic in association con dysgenese testicular pote esser si ben mascule como etiam feminin.

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SYMPTOMATIC PULMONARY DISEASE IN ARC WELDERS*

By Erwin Friede, M.D., and Donald O. Rachow, M.D., *Buffalo, N. Y.*

Many new causes of specific pneumoconiosis have been reported since the effects of deleterious substances present in various occupations have become recognized. The inhalation of noxious fumes for prolonged periods has long been known to cause lung disease whenever it occurred.

In 1936 Doig and McLaughlin [1] described striking x-ray changes after a roentgen survey of a large number of arc welders. These revealed fine nodular shadows "due to inhalation of iron dust." They noted, however, that these shadows disappeared after the removal of the patients from their occupational environment. Symptoms of fever, malaise, and cough were attributed to associated edema, which was believed to be due to the inhalation of nitrous oxide and ozone. The x-ray appearance was strikingly similar to that of silicosis; however,

* Received for publication May 21, 1959.
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it was soon evident that this type of lung disease differed markedly, and it was believed to be benign. The x-ray shadows were attributed to siderosis. Further data concerning long-term follow-up of disability of the workmen were not recorded.

Charr [2] reported numerous cases of lung disease in arc welders. Of these, three were submitted to lung biopsy. Their clinical picture showed evidence of fibrosis and pulmonary emphysema, with decreased oxygen saturation of the

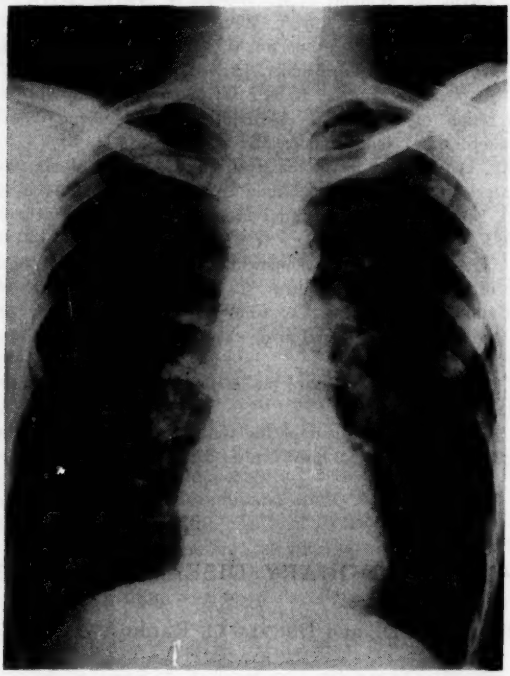

FIG. 1. X-ray of chest of patient, 9/11/57.

blood and secondary polycythemia. In this series the patients became incapacitated after long-standing exposure to arc welding fumes. No definite explanation as to the cause of the disease entity was advanced.

The purpose of this paper is to present one more case of symptomatic lung disease in arc welders, and to propose a correlation between the clinical and the pathologic findings. We shall also advance an explanation for the progressive incapacity in this particular disease.

CASE REPORT

A 40-year-old white male was admitted to the Edward J. Meyer Memorial Hospital on May 14, 1956, with the chief complaint of weakness and shortness of breath for a period of two years, and swelling of the ankles for six months.

The patient had apparently been well until approximately May, 1954, when he

noted weakness, fatigue, and exertional dyspnea, gradually increasing in severity. In October, 1955, he noted ankle edema and severe dyspnea, which led to admission for "heart failure" in another hospital. He returned to work somewhat improved, but his symptoms returned and were worse than before, requiring his present hospitalization. He denied cough, sputum, hemoptysis, or frequent infections.

The past medical history was not remarkable except for an acquired accidental deafness. In 1941, at the Johns Hopkins Hospital, where the patient was admitted for correction of this defect, studies of the heart, lungs, and blood were found to be normal.

FIG. 2. Lung biopsy. Prussian blue stain, showing thickened septa and iron pigments. × 400.

The occupational history revealed that from 1934 to 1939 the patient had worked intermittently at construction on farms, and for a few months as an arc welder. From 1945 to his present admission he had worked uninterruptedly as an electric arc welder in a poorly ventilated enclosure. During this time he worked in close proximity to the fumes, protected only by an open face mask.

Physical examination on admission revealed a well developed white male, appearing moderately cyanotic, in severe respiratory distress. Temperature, 99.5° F.; pulse, 110; respirations, 24 per minute; blood pressure, 112/70 mm. Hg. The neck veins were distended in the erect position. The chest had an increased A-P diameter and was hyperresonant. The breath sounds were distant throughout, with a few moist râles in both bases. The heart had a grade II apical systolic murmur with an increased P2. The liver was enlarged two fingerbreadths below the right

costal margin. The spleen was not palpable. The extremities showed a 4-plus pitting edema to the knees.

Laboratory studies revealed: hemoglobin, 26.1 gm.; red blood cell count, 7,500,000; hematocrit, 72%, with a normal white blood cell count and differential. The CO_2 combining power was 33 mEq./L. The arterial oxygen saturation was 46%, with a red cell mass of 441% of normal. The pulmonary function studies showed a vital capacity of 1.5 L. of a calculated normal of 4.2 L., or 36% of normal. Maximal breathing capacity was 24% of normal. The ventilatory pattern was that of marked obstruction. The electrocardiogram revealed a right axis deviation, with a P pulmonale pattern consistent with right ventricular hypertrophy and strain.

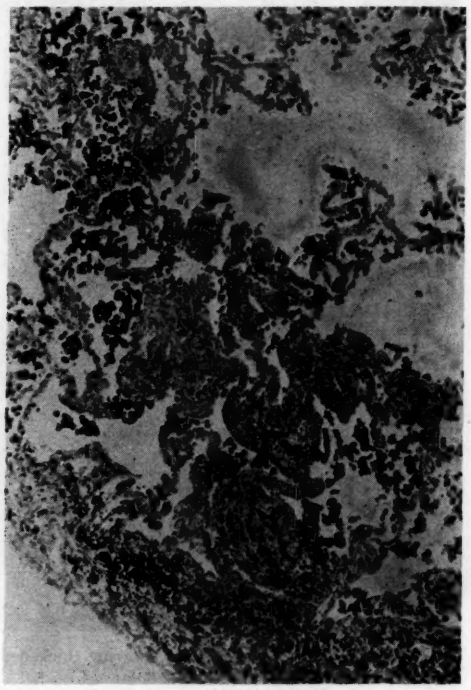

FIG. 3. Lung biopsy of different section. × 400.

During the patient's hospitalization, 4,150 ml. of blood were withdrawn. He was treated with digitalis, mercurials, and acetazolamide. After a stay of two months his arterial blood oxygenation returned to 80% of normal. Only after inhalation of 100% oxygen would his blood oxygen saturation return entirely to normal, and then for only a short period of time. Following his recovery from heart failure, new pulmonary function studies showed his vital capacity to be 2.77 L., or 60% of normal, with a timed vital capacity of 72% in three seconds. His maximal breathing capacity was still reduced to 39% of normal.

The chest x-ray (Figure 1) demonstrated a heart of normal size, with diffuse pulmonary fibrosis and a severe degree of emphysema.

After improvement a lung biopsy (Figures 2 and 3) was performed, with the

following findings: The alveolar septa were thickened, due to fibrosis, and alveoli contained macrophages loaded with brown pigment. This pigment was positive in the Prussian blue reaction, indicating iron. Similar cells with iron pigment were found in the interstitial tissue, where diffuse fibrosis was noted. Some anthracotic material was also seen. Some of the alveoli showed distention and hypertrophy of muscle fibers, with thickening of the walls of the smaller vessels.

The patient's subsequent course has been one of continuous respiratory distress and marked polycythemia. Treatment has consisted of frequent phlebotomies and correction of respiratory and cardiac failure.

Discussion

This is a case in an arc welder of severe pulmonary insufficiency due to pulmonary fibrosis, with advanced emphysema and secondary features of polycythemia and right heart strain. The emphysema is of a very severe degree, as evidenced by the obstructive pattern of the spirogram, as well as by the marked reduction of timed vital capacity and maximal breathing capacity. Fibrosis and siderosis are evident in the lung biopsy, as well as in the thickening of the walls of the smaller blood vessels, which are associated with pulmonary hypertension.

Are these permanent lung changes all due to inhalation of excessive amounts of iron, or is there another explanation that could account for them? Siderosis caused by the inhalation of iron fumes alone has until recently been believed to be benign. Recent studies have shown that excessive amounts of iron particles are carried to the interstitial spaces of the lung, setting up a mild degree of fibrosis.[3] This severe clinical picture cannot possibly be explained by excessive inhalation of iron fumes alone—other components must be present to cause such advanced disease. Studies were made of the arc welding electrode and the smoke-filled environment in which this patient worked, and the rod composition was found to be:

Carbon 0.2%
Manganese 0.9%
Phosphorus 0.04%
Sulfur 0.04%
Silicon was present.
The remainder of the composition was iron.

The rod coating consisted of:

Cellulose
Clay
Al_2O_3
Iron oxide
Manganese dioxide
A variety of silicates of sodium and magnesium, as well as possible feldspar and mica.

The quantitative analysis of the rod coating as to its silicon content indicated the following:

Total silicon 6.1%
Free silica (SiO_2) 3.4%

Emission spectrograms of the rod coating indicated the presence of the following elements:

Iron
Copper
Manganese
Magnesium
Calcium
Aluminum
Silica

Samples of the fumes were collected by millipore filters, using a Gast pump as a suction source. These samples indicated the presence of iron oxide as Fe_2O_3 in the amount of 37 mg./M^3 (suggested permissible welding fumes from ferrous material, not to exceed 30 mg./$M.^3$). A sample collected via an electrostatic precipitator indicated silica to be present in the smoke and fumes as free silica (SiO_2) to the amount of 16%. These particles in the fumes are the finest possible, and are probably less than 1μ in diameter. One is therefore confronted with two elements which will produce fibrosis in the interstitial spaces of the lung. Iron causes this to a lesser degree, free silica to a more severe and advanced degree. It is an established fact that when free silica is found in combination with iron, the fibrosing ability of the latter is markedly modified.[4] For that reason, biopsy will not show the typical picture of silicosis ordinarily seen after excessive exposure to silica dust. Instead, evidence of nonspecific fibrosis is found, which will gradually lead to emphysema and to the other secondary features of pulmonary hypertension. The advanced features of pulmonary insufficiency, as seen in this case, will become evident only after prolonged exposure to welding fumes. The concentration of these fumes must be excessive and the ventilation reduced to a minimum.

Summary

A case of symptomatic lung disease in arc welders has been discussed. The clinical picture is that of pulmonary fibrosis and advanced emphysema, with polycythemia, secondary features of pulmonary hypertension, and right heart failure. There is evidence that the explanation for the lung changes is excessive and prolonged exposure to fumes containing a combination of iron and free silica.

Summario in Interlingua

Es presentate un caso de symptomatic morbo pulmonar in un electro-soldator. Le aspecto clinic es illo de fibrosis pulmonar e emphysema avantiate, con polycythemia e le characteristicas secundari de hypertension pulmonar e disfallimento dextero-cardiac. Fibrosis e siderosis esseva evidente in le biopsia pulmonar.

Iste sever aspecto clinic non es explicabile per le inhalation sol de fumos de ferro. Le detaliate studio del electrodo de soldatura e del fumos presente in abundantia in le ambiente del patiente resultava in le constatation que silice, in le forma de silice libere, constitueva 16% del fumos. Esseva etiam presente un excesso de ferro in le forma de Fe_2O_3.

Assi duo elementos esseva identificate le quales ambes es capace a producer fibrosis in le spatio interstitio-pulmonar. Ferro causa tal fibrosis a grados minus marcate, silice libere a grados plus sever e plus avantiate.

Le explication del alterationes pulmonar se trova in le exposition excessive e prolongate a fumos que contine un combination de ferro e silice libere.

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FUNGAL ENDOCARDITIS FOLLOWING CARDIAC SURGERY * †

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The frequency of postcardiotomy endocarditis has been estimated to be less than 1%, and in the majority of the reported cases the offending organism has been *Staphylococcus aureus*.[1–4] As of this writing, only two cases of fungal endocarditis following cardiac surgery have been reported, both due to *Candida albicans*.[5, 6] This is a report of a case of *Candida parakrusei* endocarditis following aortic valvulotomy.

Case Report

A 43-year-old white male entered Passavant Memorial Hospital on May 20, 1958, with a six-months' history of palpitation, dyspnea, and syncope on marked exertion. Although he had been digitalized, the symptoms had persisted and he was admitted for cardiac evaluation. He had had rheumatic fever as a child, and was refused military service in 1941 because of a heart murmur.

On admission his weight was 143 pounds; height 5′ 7½″; pulse, 72 and totally irregular; blood pressure, 88/70 mm. Hg. Physical examination revealed the following classic findings of pure aortic stenosis: The cardiac apex was displaced to the left; a systolic thrill was palpable in the right second interspace as well as over the carotid artery; a loud, harsh systolic murmur was heard over the aortic area and was transmitted to the neck; and the second aortic sound was diminished.

* Received for publication May 22, 1959.
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The electrocardiogram was consistent with left ventricular hypertrophy and the rhythm of auricular fibrillation with premature ventricular contractions. Roentgenologic examination of the heart showed left ventricular enlargement. No intracardiac calcifications were identified. A combined left-and-right heart catheterization was performed May 21, 1958, by Dr. Paul Kezdi. The pressure gradient across the aortic valve was 116 mm. Hg. The calculated aortic valve area was 0.6 cm.^{2} There was no evidence of other valvular lesions. The marked obstruction at the aortic valve and the recent onset and progression of symptoms in this patient were considered to be indications for aortic valvulotomy.

The patient was re-admitted to Passavant Memorial Hospital on July 4, and on July 9, 1958, a transaortic commissurotomy was performed with the aid of a membrane oxygenator and moderate hypothermia (32° C.). Two of the aortic valve commissures were found to be obliterated, producing a significant stenosis, and there were moderate calcification of one cusp and slight calcification of the other two. One commissure was opened with a pair of scissors, thus producing a competent bicuspid valve.

The patient withstood the procedure well. Except for a low grade fever lasting four days, the postoperative convalescence was satisfactory. A blood culture during the period of fever was negative. Nine units of whole blood were used during surgery and the following 24-hour period. As prophylaxis, he had received 600,000 units of procaine penicillin intramuscularly daily for the four days prior to surgery. Postoperatively he received 400,000 units of procaine penicillin twice daily, and 0.5 gm. of dihydrostreptomycin twice daily during the remainder of his hospital stay. Antibiotic therapy was discontinued, and the patient was discharged July 27, 1958, 18 days after surgery.

Six weeks after surgery the patient noted the gradual onset of anorexia, malaise, jaundice, darkening urine, and clay-colored stools. He was re-admitted to Passavant Memorial Hospital on August 27, 1958. He appeared to be chronically ill and jaundiced. The temperature was 99° F.; weight, 127 pounds. The liver was enlarged.

The urine was a dark amber color and weakly positive for bile. The hemoglobin was 13.5 gm., and the erythrocyte sedimentation rate was 25 mm. (Wintrobe). The blood chemistries showed alkaline phosphatase, 12.1 Bodansky units; total serum bilirubin, 4.84 mg.%; direct bilirubin, 2.06 mg.%; cephalin flocculation, 3-plus in 24 hours, and 4-plus in 48 hours; thymol turbidity, 3.56 units; serum total proteins, 5.69 gm.%, with albumin, 3.18 gm.%, and globulin, 2.51 gm.%; and cholesterol, 183 mg.%

The diagnosis was serum hepatitis, and the patient was treated with bed-rest and a high carbohydrate diet. His symptoms diminished, and he was discharged to convalescence at home on September 3, 1958.

The patient was re-admitted on November 16, 1958. For the month prior to admission he had complained of persistent weakness, malaise, anorexia, and further weight loss. His only medication had been 0.1 mg. digitoxin daily. He was thin and lethargic, and appeared to be severely ill. The pulse rate was 103/min. and totally irregular; blood pressure, 110/70 mm. Hg; temperature, 100° F.; weight, 118 pounds. He was not jaundiced, and there was no evidence of peripheral embolization. The cardiac findings were unchanged. Neither the liver nor the spleen was palpable.

The urine sediment showed 10 red blood cells per high power field and 45 white blood cells per high power field in a centrifuged specimen. The urine culture was negative. The red blood count was 3,920,000; hemoglobin, 11.6 gm.; hematocrit, 35%; white blood count, 5,050 (87 neutrophils, 8 lymphocytes, 5 monocytes); erythrocyte sedimentation rate, 33 mm. (Wintrobe). The blood chemistries showed alkaline phosphatase, 3.44 units; total serum bilirubin, 0.77 mg.%; cephalin floccula-

tion, 3-plus in 24 hours and 4-plus in 48 hours; thymol turbidity, 14.7 units; total serum protein, 5.64 gm.%, with albumin, 2.61 gm.%, and globulin, 3.03 gm.%; serum glutamic-oxalacetic transaminase, 29 units; blood urea nitrogen, 10.3 mg.%.

The diagnosis of subacute bacterial endocarditis was considered, and multiple blood cultures were taken. After four days' incubation, all blood cultures revealed a pure growth of *C. parakrusei*. Amphotericin B (Fungizone) was administered intravenously in increasing increments, diluted in 1,000 ml. of 5% dextrose in water. A dose of 1.5 mg. per kilogram of body weight per day was gradually attained and continued (Figure 1). Amphotericin B therapy resulted in an increase of blood urea nitrogen without increase in proteinuria or formed elements in the urine sediment. Other toxic effects of the drug were not observed (i.e., gastrointestinal

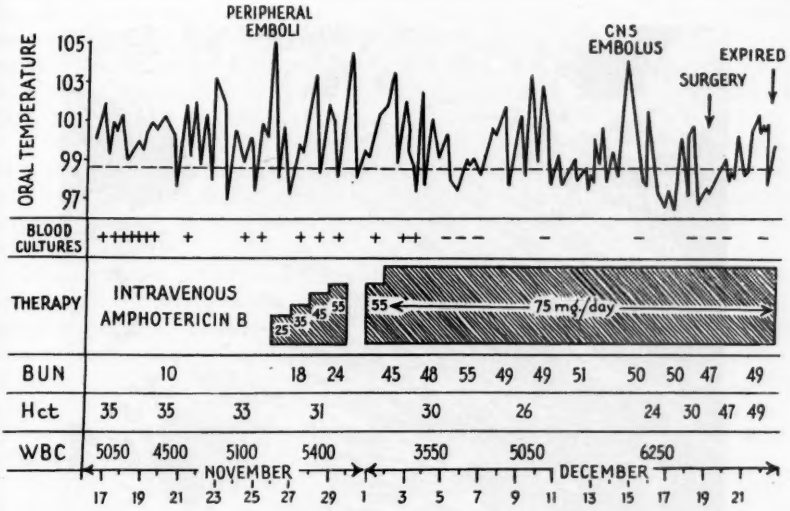

FIG. 1. Hospital course.

hemorrhage, headache, nausea, vomiting, and phlebitis). The azotemia was not considered to be severe enough to discontinue therapy. In vitro studies showed amphotericin B to be fungistatic for *C. parakrusei* at the level of 0.1 to 0.2 μg./ml., and fungicidal at the level of 1.5 to 3.0 μg./ml. After seven days of therapy, nine subsequent blood cultures were sterile for the remainder of the course. Oral nystatin (Mycostatin) had been administered before parenteral amphotericin B was available, but was discontinued after the latter drug had been administered in full doses.

Ten days after admission, and before amphotericin B was administered, the patient had a sudden temperature elevation to 105° F., and multiple petechiae were evident in the conjunctivae, retinae, hard palate, and distal phalanges. Although fever persisted, the patient was subjectively improved after one week of amphotericin B therapy. However, on December 15 he complained of the sudden onset of diplopia. Examination at that time revealed lesions of the right III and left VI and VII cranial nerves and a left hemiparesis. This combination was considered to be the result of an embolus to the brain stem. Thereafter his condition rapidly deteriorated, and he became anorectic and semicomatose.

In view of a recent report,[7] the surgical service considered the possibility that

an aortic suture abscess could be the site of infection. Removal of suture abscesses had been known to result in cures of such infections. Despite sterilization of the blood by amphotericin B, ultimate sterilization and healing of large fungal vegetations were considered to be only remote possibilities if the lesion was valvular rather than due to infected sutures. For these reasons, the aortic valve area was re-explored on December 20, 1958. This operation was a direct-vision exposure of the aortic valve during hypothermia with inflow occlusion. The sutures placed in the right and left atria at the first operation were not infected. Sutures in the aorta were not infected, but they were excised, along with a small aneurysm found at the base of the aortic incision. Large, friable vegetations, measuring 12 by 7 by 5 mm., were found on the aortic valve and were removed. A culture of the vegetations revealed a pure growth of *C. parakrusei*. Sections of these vegetations showed dense, matted threads

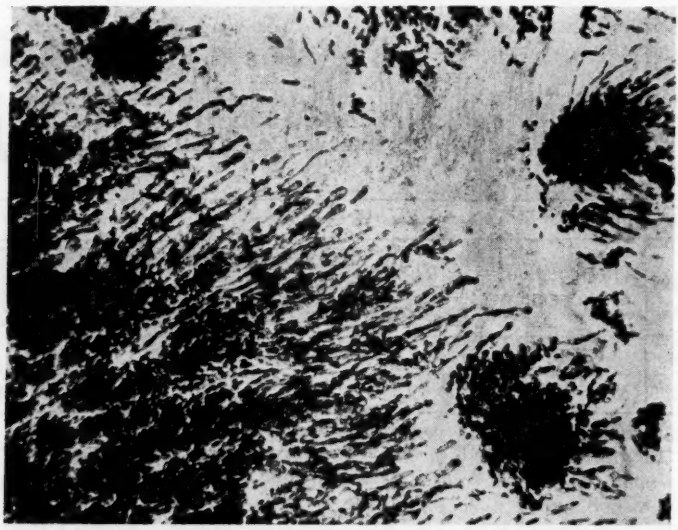

FIG. 2. Microscopic picture of aortic valve vegetation, showing pseudomycelia and many oval, single, and budding cells of *Candida parakrusei*. Periodic acid Schiff stain; × 600.

with the characteristic morphology of *Candida* colonies (Figure 2). The subsequently "clean" aortic valve appeared to function well. Ventricular fibrillation occurred and was electrically controlled. After the chest had been closed the left leg appeared to be cyanotic and cold, and so the left popliteal artery was exposed and an arteriotomy made. No embolus was found, and circulation to the leg remained poor.

The patient was sent to the recovery room, where he experienced runs of ventricular tachycardia. Sixty hours after surgery he suffered cardiac arrest while his tracheotomy tube was being suctioned, and he died on December 22, 1958. Permission for a post-mortem examination was denied.

COMMENTS

The *C. parakrusei* reported to be growing in the blood culture of this patient was initially interpreted as a contaminant. However, when seven consecutive

blood cultures yielded the same organism, and blood cultures from other patients taken during this period were not positive for fungus, the diagnosis of *Candida* septicemia was confirmed. Though there were no new or changing heart murmurs, the history of heart surgery and the development of peripheral emboli indicated the diagnosis of endocarditis. The onset of symptoms was three months, the diagnosis was made approximately four months after aortic valvulotomy, and death occurred five and one-half months after surgery. In the two previously reported cases, both due to *C. albicans,* the diagnosis in one was made ante-mortem three months after surgery,[5] and in the other the diagnosis was not made until post-mortem examination, three months after surgery.[6]

A local site of fungal infection which may have given rise to hematogenous spread was not identified in the present case. In view of the relatively long interval between the heart operation and the diagnosis of endocarditis, it is not certain that the infection was caused by the operation. However, there would certainly be a possibility of contamination at that time, and this organism is characteristically a slow-growing one.

Twelve cases of *Candida* endocarditis have been reported, three due to *C. parakrusei.*[6, 8-12] Although *C. parakrusei* is normally nonpathogenic, the pathogenicity may rise if host resistance is reduced.[13] The cardiac surgery and the hepatitis probably contributed to debilitation of the patient and lowering of host defenses.

The antibiotic prophylaxis employed during the initial aortic valvulotomy included dihydrostreptomycin and penicillin, given for 18 days during the postoperative period. The use of both antibiotics may have altered the normal flora of the oral cavity and digestive tract to permit overgrowth of *Candida* organisms, an event that has occurred when chemotherapy was directed against a broad spectrum of gram-positive and gram-negative organisms.[14, 15] No studies were made, however, following the initial surgery, to determine whether a change in normal flora had occurred.

Such cases as the one reported raise the question of the appropriate chemoprophylaxis of endocarditis in extensive cardiac surgery. Perhaps more modest doses of penicillin, in the range recommended by the American Heart Association [16] for the usual prophylaxis of subacute bacterial endocarditis, would prevent infection by most common pathogens without predisposing to overgrowth of normal flora by *Candida.*

Amphotericin B is derived from an as yet unidentified species of *Streptomyces,* and has been used successfully in a variety of systemic fungus infections.[17] Results of its use in generalized moniliasis have been encouraging,[18] although there have been no reported cures of *Candida* endocarditis. The maximal recommended daily dose was used in the case reported above, and after seven days of therapy, blood cultures were sterile.

If the studies of Smith and Wood [19] are applicable to the effect of amphotericin B on *Candida,* the organisms are destroyed only in areas where they are multiplying rapidly. A recent report by McNall [20] indicates that *Candida* organisms are killed by amphotericin B in proportion to their rate of growth, a situation similar to that of penicillin and penicillin-sensitive organisms. Conditions of optimal growth do not exist in an abscess. The occurrence of infected silk granulomas in the heart and great vessels after surgery is well recognized.[7] Prompt cures have been effected by removal of the sutures and any necrotic

material. Because of the nature of the lesion in our patient, prolonged therapy undoubtedly would have been necessary for ultimate sterilization of the huge, matted vegetations. The patient's condition was rapidly deteriorating, and it did not seem that he could survive prolonged treatment. He had irregular spikes of fever and evidence of major artery emboli. Therefore, to hasten the bacteriologic cure and prevent further embolic phenomena, the aortic valve area was explored surgically in the hope of finding a reversible lesion.

Unfortunately, the site of the lesion was on the valve surfaces rather than in infected sutures and showed the characteristic huge, friable vegetations commonly found in *Candida* endocarditis.[12] It is of interest that excision of these lesions was accomplished, leaving behind a relatively "clean" valve surface. Had the patient's condition not been so poor, continuing amphotericin B therapy after surgery might have prevented further fungal growth and provided a better opportunity for ultimate cure. It is interesting to speculate whether surgical debridement might ultimately be part of successful treatment of some forms of endocarditis.

Summary

A case of *Candida parakrusei* endocarditis following aortic valvulotomy is described.

Acknowledgment

The authors are indebted to Dr. Gene H. Stollerman for his advice and consultation in the preparation of this report; and to Dr. Milton Silverman and Rosemary Brunst, of the Veterans Administration Research Hospital, Chicago, Illinois, for their assistance in identifying this fungus.

Summario in Interlingua

Es presentate un caso de endocarditis post-cardiotomic causate per *Candida parakrusei*. Le patiente, un masculo de racia blanc de 43 annos de etate, entrava in le hospital con le gravamines de palpitation, dyspnea, e syncope post effortio major. Le examine physic e le constatationes laboratorial—incluse un combinate catheterisation dextero-sinistro-cardiac—esseva compatibile con le diagnose de pur stenosis aortic.

Le 9 de julio 1958, un commissurotomia transaortic esseva effectuate, e un competente valvula bicuspidic esseva create. Novem unitates de sanguine total esseva usate durante le operation. Post le operation le patiente recipeva 400.000 unitates de penicillina a procaina duo vices per die e 0,5 g de dihydrostreptomycina etiam duo vices per die durante un periodo de 18 dies. Sex septimanas post le chirurgia, le patiente esseva re-admittite con hepatitis seral. Ille se restabliva ab iste maladia e esseva dimittite ab le hospital pro completar su reconvalescentia a su domicilio. Isto esseva le 3 de septembre 1958. In octobre del mesme anno le patiente se plangeva de persistente debilitate, malaise, anorexia, e perdita additional de peso. Ille esseva rehospitalisate le 16 de novembre 1958. Nulle signos de endocarditis esseva evidente a iste tempore, sed multiple culturas sanguinee esseva executate. Post un incubation de quatro dies, omne le culturas de sanguine revelava un crescentia pur de *C. parakrusei*. Le curso del patiente al hospital esseva febril. Dece dies post su admission, multiple petechias esseva apparente. Amphotericina B, diluite in 1.000 ml de 5% de dextrosa in aqua, esseva administrate intravenosemente in doses progressivemente plus grande. Gradualmente le dosage esseva augmentate usque al nivello de 1,5 mg per kg de peso corporee e mantenite illac (tabula 1).

Studios in vitro monstrava que amphotericina B esseva fungistatic pro *C.*

parakrusei al nivello de inter 0,1 e 0,2 μg/ml e fungicida al nivello de 1,5 a 3,0 μg/ml. Post septe dies de iste therapia, novem culturas sanguinee esseva prendite e se provava sterile durante le resto del curso clinic. Tamen, le phenomenos embolic persisteva, e le 15 de decembre signos esseva manifeste de un embolo al caudice cerebral. Le condition del patiente se deteriorava rapidemente. Ille deveniva anorectic e semicomatose.

Un abscesso in le sutura aortic esseva considerate como un sito possibile de infection. In despecto del sterilisation del sanguine per amphotericina B, le effectuation de un sterilisation complete e de un restitution total ab major vegetationes fungose esseva considerate como pauco probabile in caso le lesione esseva valvular plus tosto que un question de suturas inficite. Pro iste rationes, le area del valvula aortic esseva re-explorate le 20 de decembre 1958. Le suturas non esseva inficite, sed friabile vegetationes de 12 per 7 per 5 mm in dimension esseva trovate super le valvula aortic. Illos esseva excidite (figura 1). Un cultura del vegetationes revelava un crescentia pur de *C. parakrusei*. Le 22 de decembre 1958, 60 horas post le operation, le patiente suffreva arresto cardiac e moriva.

Isto es le tertie reportate caso de endocarditis fungal post chirurgia cardiac. Le duo previemente reportate casos esseva ambes causate per *C. albicans*. A causa del relativemente longe intervallo inter le operation e le diagnose de endocarditis in le caso del presente reporto, il non es certe que le infection esseva le resultato del operation. Le uso del duo antibioticos durante le aorto-valvulotomia initial ha possibilemente alterate le flora normal del cavitate oral e del vias digestive con le effecto de un crescentia excessive del organismos de candida. Il es de interesse que le excision del vegetationes ab le valvula aortic esseva effectuate con le resultato de un relativemente nitide superficie valvular. Il pare possibile que un forma de debridement chirurgic va establir se in le curso del tempore como un mesura acceptate in le tractamento de certe typos de endocarditis.

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MYELOMATOSIS WITH XANTHOMATOSIS *

By Boy Frame, M.D., M. R. Pachter, M.Sc., M.D.,† and R. K. Nixon, M.D., *Detroit, Michigan*

During the last decade considerable attention has been focused on the serum protein aberrations in multiple myeloma.[1] Little information has been presented, however, regarding the serum lipids and the possibility of deranged lipid metabolism in this disease. Kanzow,[2] in evaluating 10 patients with macroglobulinemia of Waldenström and five with myelomatosis, observed a marked decrease in serum lipids in a majority of these cases, especially in those with macroglobulinemia. Similar findings of strikingly low cholesterol values in patients with multiple myeloma were noted by Leibetseder,[3] Gross and Weicker,[4] and Lewis and Page.[5] Still other authors have substantiated the presence of low cholesterol levels in certain patients with macroglobulinemia.[6]

Hypercholesterolemia as a feature of myelomatosis has been reported by Hill et al.,[7] Sachs et al.,[8] and Waldenström.[9] This relationship has, however, been more commonly observed in cases of myeloma that were superimposed upon

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an already existent nephrotic state.[2] It remained for Spain et al.[10] to correlate depression of the S_f 12–20 and S_f 20–100 lipoproteins with the remarkable minor degree of atherosclerosis presented by patients with myelomatosis.

Lennard-Jones [11] records what is believed to be the first case of myeloma associated with skin xanthomata and elevated serum lipids. In a personal communication to the authors,[12] Lennard-Jones mentions knowledge of three additional patients with myeloma and lipemic serum, but without integumentary xanthomata. The purpose of the present article is to report what appears to be the second recorded case of a patient presenting the clinical picture of multiple

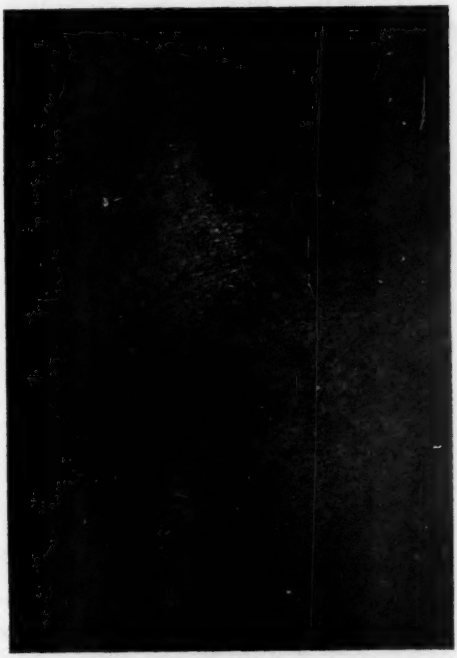

FIG. 1. Skin of lateral neck region, demonstrating a diffuse, slightly raised infiltration that was distinctly yellow in color.

myeloma as well as hyperlipidemia and skin xanthomata. Some of the known and theoretic relationships between elevated serum lipids and hyperglobulinemia as related to the patient under consideration will be discussed.

CASE REPORT

A 59-year-old farmer was seen in the out-patient department of the Henry Ford Hospital with the complaint of having had five episodes of pneumonia during the last four years. He had recovered completely from his last bout of pneumonia (two months earlier), and was now asymptomatic. There was no past history of hypertension, angina, or cerebral vascular accidents. Family history was negative for evidences of vascular disease and skin xanthomata. Cholesterol determinations carried out in two sons, four brothers, and one daughter were within normal limits.

Physical examination revealed a well developed male with a diffuse, slightly raised yellow infiltration of the skin (Figure 1) in the following regions: supraorbital areas, lateral areas of the neck, axillae, lower abdomen and flanks, and especially about appendectomy and herniorrhaphy scars. Palmar creases and plantar surfaces of the feet were normal. The patient had not been aware of the skin changes, but his wife thought they had been present for about one year. Blood pressure was 125/75 mm. Hg. Eyegrounds were negative for evidence of vascular disease. The remainder of the physical examination was within normal limits. There was no bone tenderness.

Laboratory data included a white blood cell count of 6,350 per cubic millimeter, and a hemoglobin of 11.5 gm.%. The urine specific gravity was 1.017; albumin, 1-plus; Bence Jones protein, negative; sediment, normal. The result of the serologic

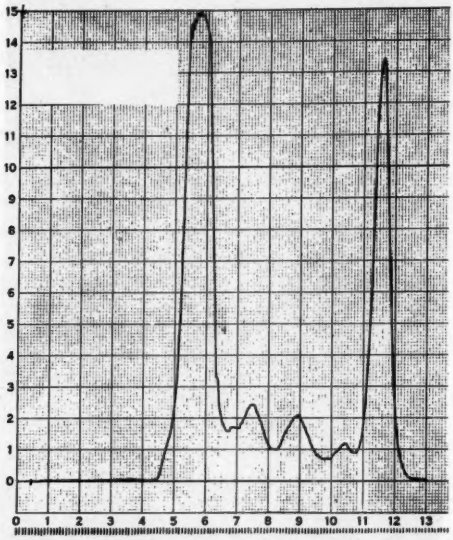

FIG. 2. Paper electrophoresis pattern of patient. The direction of migration is from right to left, and reveals a tall, slender, narrow-based peak in the γ position.

test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was negative. Fasting blood sugar was 80 mg.%. Bromsulfalein test, negative; one minute bilirubin, 0.4; total bilirubin, 0.8 mg.%. Serum calcium, 9.5; inorganic phosphorus, 3.8 mg.%. Total cholesterol, 538 mg.% (normal, 140 to 280 mg.%), with 64% esters. Total lipids were increased to 1,370 (normal, 400 to 650), and phospholipid phosphorus to 58 mg.% (normal, 8 to 11 mg.%). The serum was clear after standing. Protein-bound iodine was 5.1 μg.%. Electrophoretic pattern of serum proteins revealed 9.2 gm. total; 2.26 gm. albumin; 0.23 gm. alpha$_1$; 0.62 gm. alpha$_2$; 0.74 gm. beta; 5.35 gm. gamma globulin (Figure 2). Cryoglobulins were 3-plus at the end of 72 hours. Ultracentrifugal studies on the whole serum as well as on the isolated cryoglobulins failed to reveal any macromolecular proteins. An L. E. test was negative. Coagulation studies revealed a prothrombin time of 17 sec. (control, 15 sec.); Lee-White coagulation time, 7½ and 9½ min.; prothrombin consumption, 20 sec. (normal, over 30 sec.; abnormal,

20 sec. or under); plasma clotting time, 98 sec. (normal, 90 to 150 sec.); and an absence of gross fibrinolytic activity. Bone marrow (Figure 3) revealed a diffuse increase (to 50%) of immature plasma cells. Radiologic survey of the skeleton showed no lytic lesions or demineralization. Chest x-ray revealed an indistinct infiltrate in the right lower lobe. An electrocardiogram was normal.

The patient returned to his home, and was subsequently admitted to an outside hospital, where he died from overwhelming pneumonia complicated by shock. His premature death precluded the further lipoprotein evaluations that had been planned.

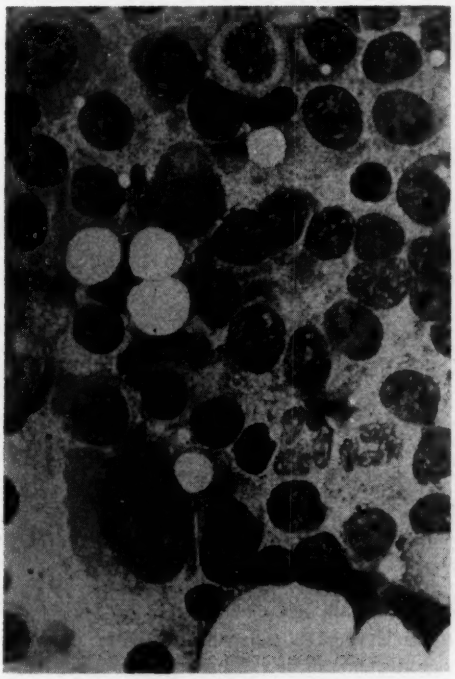

FIG. 3. Bone marrow aspirate, demonstrating marked predominance of immature plasma cells (myeloma cells), as well as malignant plasma cells. Leishman's stain, magnification × 100.

Pathology: Biopsy of skin lesions from the left supraclavicular and left flank areas demonstrated linear accumulations of xanthoma cells in the upper dermis (Figure 4). Sudan black IV stain on formalin-fixed frozen section of the xanthomata showed large amounts of lipid in the xanthoma cells.

Autopsy (Prosector: Dr. O. Lohr, of Saginaw, Michigan): Right and left lungs revealed a marked degree of necrotizing bronchopneumonia, with accompanying fibropurulent pleuritis. The heart demonstrated a fibrinopurulent pericarditis, with large amounts of pus in the pericardial sac, mild muscle hypertrophy, and minimal coronary sclerosis. Culture of the pericardial pus revealed staphylococci (not further defined). Liver and kidneys were moderately congested. Other organs showed congestion and mild arteriosclerosis, but were otherwise unremarkable. Bone marrow aspirates taken at autopsy revealed 43% immature plasma cells.

Discussion

Despite the well documented cases of paraproteinemia accompanied by either hypolipidemia, normolipidemia [13] or hyperlipidemia that have appeared in the literature, no suitable hypothesis has evolved to explain or to attempt to correlate the alterations in the protein metabolism with those found in the lipid metabolism. The electrophoretic mobility and the molecular weight of the individual proteins involved does not appear to be of paramount importance, since abnormal lipid values have appeared with normomolecular as well as macromolecular beta and gamma hyperglobulinemia.

In respect to the lipoproteins, Lewis et al.[15] with the aid of ultracentrifugal analysis, observed no correlation between changes in serum protein pattern and lipoprotein distribution. Conversely, Sachs [8] and his co-workers reported that

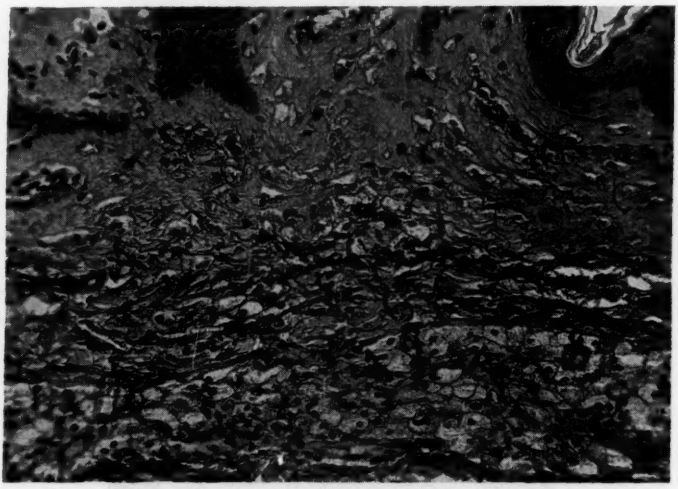

Fig. 4. Skin of left flank. Pockets of xanthoma cells in upper dermis. Hematoxylin and eosin, magnification × 300.

lipids were concentrated in the fraction which was pathologically increased. This diversity of findings may well be based on the variation in the technical tools used in the individual studies. It is generally assumed [14] that lipids are adsorbed on the serum proteins; therefore, the very presence of hyperglobulinemia, with consequent increase of available protein for lipid transport, in certain cases of paraproteinemia might be used to explain the hyperlipidemia. That mere elevation of protein, however, is not sufficient to explain increased blood serum lipid values is attested to by Kanzow's work.[2] In these latter evaluations of serum lipids in patients with increased gamma globulins secondary to liver cirrhosis, no consistent alteration was noted in the lipid fractions. Furthermore, hyperglobulinemia as a cause of hyperlipidemia would still not explain those cases presenting with hypolipidemia or normolipidemia. This latter objection might be overcome by proposing that quantitative increase had to be coupled with specific qualitative alterations of the proteins involved before hyperglobulinemia

would serve to explain hyperlipidemia. At present, no experimental evidence is available to support the thesis that variation in serum lipid values, in individual cases of paraproteinemia, is secondary to qualitative changes in serum proteins.

The question as to whether a poor nutritional status of patients with myelomatosis or macroglobulinemia might account for hypolipidemia is negated by the relatively good nutritional state noted in many of these patients.[2] Since it is known [14, 15] that the liver and thyroid have an effect on serum lipids, the functional activity of these organs in any given case should be evaluated so as to rule out their potential pathogenetic role.

In the present case, one possible explanation of the hyperglobulinemia and the hyperlipidemia is immediately forthcoming: a fortuitous occurrence of two disease entities without a common etiology. The multiple myeloma, clinically present for four years, may simply have been joined three years later by the skin xanthomata and the hyperlipidemia. Unfortunately, we do not know how long the hyperlipidemia was present, and whether its increase coincided with the appearance of the skin lesions. Familial serum lipid elevation, at least as measured by the level of serum cholesterol, was not present. That abnormal thyroid and liver functions were not involved in this situation is adequately attested to by the laboratory data. The nutritional status of the patient was not significantly altered to nominate this factor for etiologic consideration. Of importance is the fact that the patient's hyperglobulinemia fell in the gamma range, while most lipid-carrying proteins are members of the alpha or beta groups.

It would appear, at present, that individual cases of paraproteinemia may demonstrate a wide spectrum of serum lipid values. The basis for this variability may simply lie in the realm of biologic variation. On the other hand, it is known that the proteins produced in each individual case of multiple myeloma appear to differ from those found in another.[16] Thus, it may well be that in an individual case the myeloma cells, and perhaps the lymphoid-reticulum cells of macroglobulinemia, may be so qualitatively altered as to lead to either a hypolipidemia, a normolipidemia or a hyperlipidemia. In this respect Lennard-Jones [12] noted that the serum of his patient contained an excess of beta lipoprotein—possibly, he postulates, as a product of the myeloma cell. That the myeloma cells in a given case may produce lipid accumulations has been suggested by Hollan.[17] He observed a case of myelomatosis with an abnormal lipoprotein fraction and a high percentage of myeloma cells which were surrounded by a lipid-staining substance. Unfortunately, the unexpected death of our patient precluded any attempt at further evaluations, particularly in regard to lipoproteins and lipid stains of the bone marrow.

Needless to say, more specific statements concerning the potential intimate relationship between lipid and protein metabolism in multiple myeloma will have to await further clinical and laboratory evaluations.

Summary

A case is presented in which myelomatosis was associated with hyperlipidemia and skin xanthomata. Discussion of the deranged lipid and protein fractions in the patient's serum is related to previously recorded serum lipid changes in multiple myeloma. It is possible that, in certain cases of myeloma, the plasma cells may directly produce abnormal lipid fractions, or that a sufficiently abnormal

lipid-binding protein is secreted to account for the serum lipid aberrations in the disease.

SUMMARIO IN INTERLINGUA

In recente annos multe attention ha essite prestate al alterationes del proteinas seral in myeloma multiple. Le possibile disrangiamento del lipidos del sero in ille morbo ha non recipite le mesme tractamento. Es reportate le caso de un patiente qui habeva myeloma e simultaneemente generalisate xanthomatosis e hyperlipemia. Le cholesterol total esseva 538 mg%; le lipidos total, 1.370 mg%; le phosphoro phospholipidic, 58 mg%. Determinationes de proteina seral revelava un nivello total de 9,2 g% e 5,35 g% pro globulina gamma. Le medulla ossee contineva 50% de immatur plasmocytos. Un biopsia cutanee demonstrava cellulas xanthomatic in le derme superior.

Le discussion del perturbate fractiones lipidic e proteinic in le sero del patiente es ponite in relation con previemente observate alterationes del lipidos seral in myeloma multiple. Il es possibile que in certe casos de myeloma le plasmocytos produce anormal fractiones lipidic directemente o etiam que un proteina sufficientemente anormal es secernite pro explicar le aberrationes del lipidos seral.

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PULMONARY ALLESCHERIASIS *

By Richard E. Travis, M.D., Elizabeth W. Ulrich,† and Samuel Phillips, M.D., F.A.C.P., *Memphis, Tennessee*

Certain fungus infections are usually found in association with other primary diseases. The most common of these are moniliasis, aspergillosis, and mucormycosis. According to Zimmerman,[1] three factors may be responsible for the occurrence of these infections: a general state of increased susceptibility due to the primary disease; a local lesion, usually in the lungs or gastrointestinal tract, which the fungus can use as a portal of entry; and an ecologic disturbance, brought about by various antibiotics, the corticosteroids, and perhaps other drugs used in the treatment of the primary disease or its complications.

Our case appears to be a good illustration of the above factors, and is of particular interest because, to our knowledge, it is only the second case of pulmonary allescheriasis ever reported.

Case Report

A white male farmer was 30 years old when he first developed cough, left chest pain, fever, and malaise in December, 1950. He had previously been in good health. He was treated with penicillin and improved, but his malaise persisted. In April, 1951, all symptoms recurred, but again subsided following penicillin therapy. However, a chest x-ray was obtained and the findings were suggestive of pulmonary tuberculosis. The patient was referred to a Veterans Administration tuberculosis hospital on May 29, 1951, but was transferred to our hospital a few days later as a diagnostic problem. Slight cough and easy fatigability were the chief complaints at this time. The patient appeared to be well developed and well nourished. There was slight tracheal deviation to the left, a few moist râles were heard over the apex of the left lung posteriorly, and a nontender liver edge was barely palpable at the right costal margin. Otherwise, the findings on physical examination were negative. The chest x-ray showed linear and mottled infiltrates in the upper halves of both lung fields, bullae in the apices, and a radiolucency in the left upper lung field, as illustrated in Figure 1. Skin tests were negative for tuberculosis, blastomycosis, coccidioidomycosis, and histoplasmosis. Sputa and gastric washings were negative

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for tubercle bacilli by repeated examinations, including culture. Sputum cultures for fungi on three examinations yielded only *Candida albicans*. Bronchoscopic examination revealed mild generalized hyperemia of the bronchial mucosa. Bronchial washings were negative for tubercle bacilli and fungi.

A lung biopsy was obtained on July 6, 1951, which on microscopic examination showed nodules composed of giant cells and epithelioid cells, with surrounding dense hyaline fibrosis in many of the alveolar walls. There was coalescence of nodules

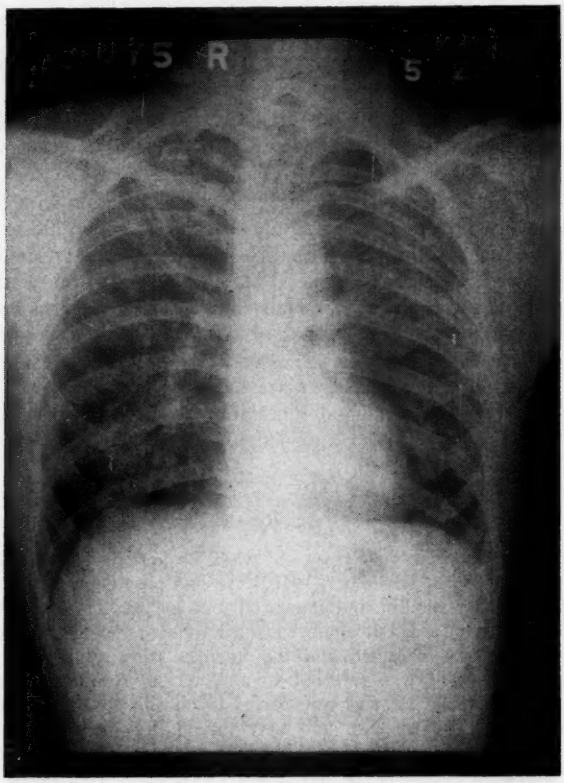

FIG. 1. Chest x-ray made during initial hospitalization—five months after onset of symptoms.

in some areas, but no caseation or necrosis. No inclusion bodies were seen. Periodic acid-Schiff stain showed no evidence of fungi. Cultures taken from the lung biopsy specimen were negative for tubercle bacilli and fungi. X-rays of the hands and feet appeared to be normal, as were the serum calcium and proteins. Although sarcoidosis was considered to be the most likely diagnosis, the patient was placed on streptomycin and para-aminosalicylic acid (PAS) because pulmonary tuberculosis was still a possibility. However, the patient left the hospital against medical advice on August 25, 1951, shortly after administration of these drugs was started, and did not continue the medication.

The patient was seen periodically over the next two years, and seemed to show no significant change. Chest x-rays were stable in appearance. The skin tests remained negative. One isolated sputum culture was reported to be positive for tubercle bacilli on January 30, 1953, as were occasional cultures for *C. albicans*. These were not considered to be significant.

In November, 1953, more than two years after the initial hospitalization, the patient experienced the first of many bouts of hemoptysis and was rehospitalized. He

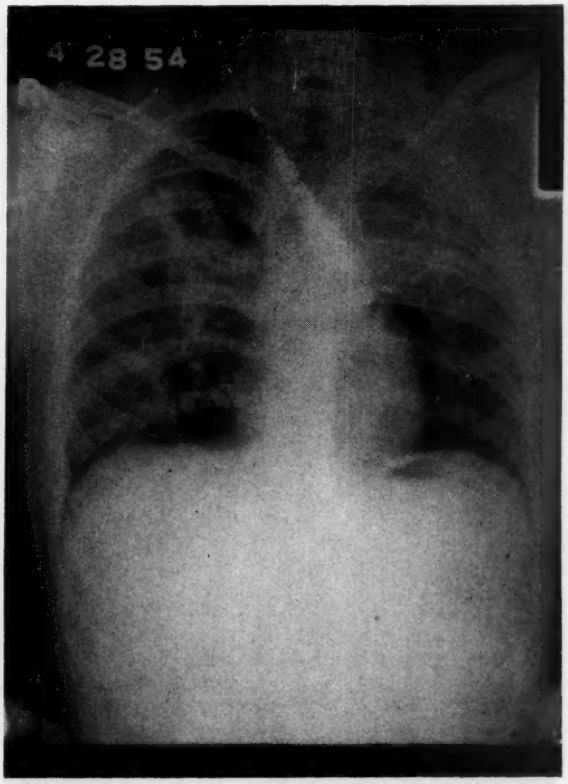

FIG. 2. Chest x-ray just prior to corticosteroid therapy. Note progression of disease since first x-ray.

complained of dyspnea on exertion. The chest x-ray revealed progression of disease, and multiple thin-walled radiolucencies were noted in both upper lung fields (Figure 2). The Mantoux test was still negative, and no tubercle bacilli could be found in the sputum. ACTH and then cortisone were given from May until August, 1954, and although little subjective improvement was noted, the chest x-rays showed moderate clearing (Figure 3). X-ray diffraction studies made on the sputum and on the lung biopsy specimen obtained in 1951 were found to be negative for silicosis and berylliosis. Serologic tests for blastomycosis, coccidioidomycosis, and histoplasmosis either were negative or were positive in a nonsignificant titer. Although hemoptysis

and pulmonary cavitation are not commonly described in sarcoidosis, the evidence now seemed predominantly in favor of this diagnosis, and the patient was discharged as having sarcoidosis, improved, in August, 1954.

Repeated hemoptyses, progressive dyspnea on exertion, and recurrent respiratory infection forced the patient to be rehospitalized four times between December, 1954, and July, 1955. Cortisone was started again in December, 1954, and was continued in a maintenance dose of 50 mg. daily. Short courses of penicillin or tetracycline were also given whenever the sputum became purulent.

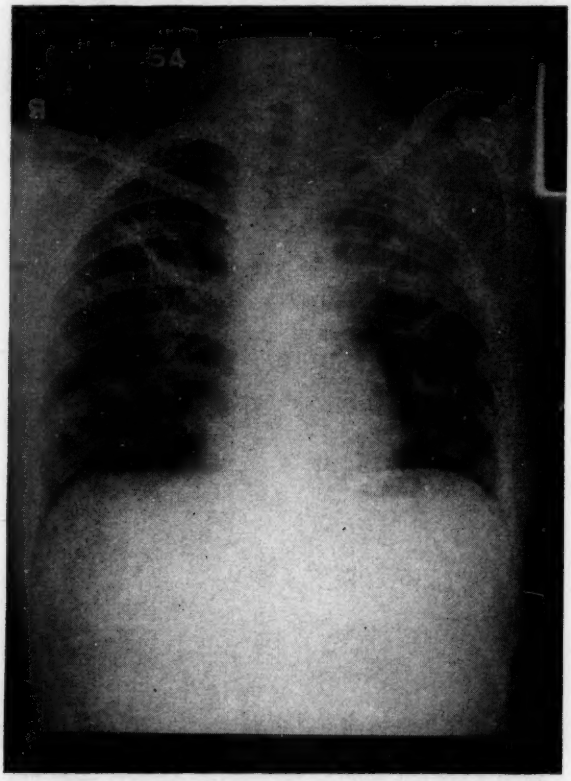

FIG. 3. Chest x-ray, showing moderate clearing after one month of corticosteroid therapy.

The patient's final admission, on October 22, 1955, was again prompted by hemoptysis. He appeared to be acutely ill and markedly dyspneic. The chest contour was emphysematous, and its expansion was greatly diminished. Scattered râles, rhonchi, and wheezes were heard over both lung fields. P_2 was accentuated and greater than A_2. Moderate clubbing of the fingers and toes was noted, and there was a trace of pedal edema bilaterally.

Throughout this period of hospitalization the patient remained bedridden because of respiratory insufficiency and recurrent hemoptyses. Corticosteroid therapy was maintained with cortisone until April, 1956, when it was changed to prednisone, 12.5

mg. daily. Attempts to reduce the dosage below this level were unsuccessful because of dyspnea. Many courses of the various antibiotics were given because of repeated bronchopulmonary infections. The sputum was examined at monthly intervals for tubercle bacilli and fungi, and remained negative except for *C. albicans,* until February 6, 1957, when *Monosporium apiospermum* was isolated. On further laboratory study the same fungus also was obtained in its other form, *Allescheria boydii.* This organism was repeatedly cultured from sputum specimens obtained between February and November, 1957. Four blood cultures during this interval were negative. A

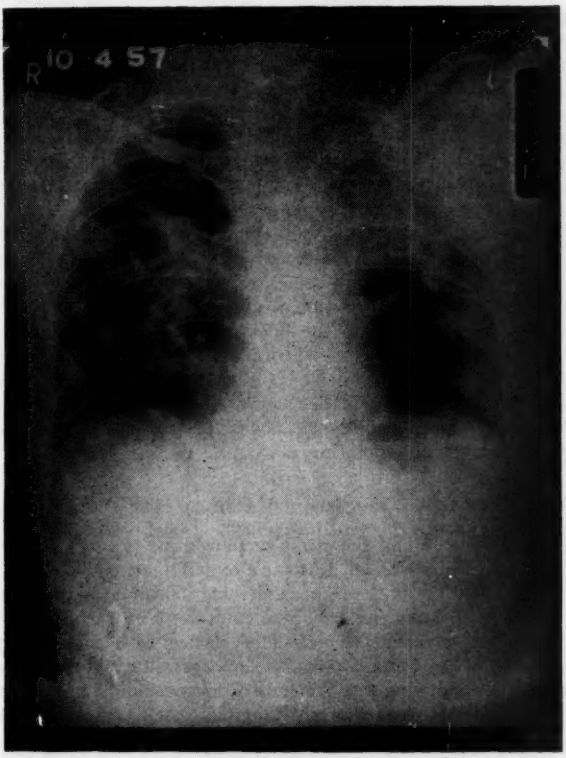

FIG. 4. Chest x-ray two months prior to death, showing extensive involvement of both lungs.

scalene node biopsy performed on April 9, 1957, was consistent with sarcoidosis on microscopic examination, showing nodules composed of epithelioid cells and giant cells, with no caseation necrosis. The cultures taken from this tissue were negative for fungi and for tubercle bacilli. Serial chest x-rays revealed progressive fibrosis. There were also enlargement of the radiolucencies in both upper lung fields and marked thickening of the left apical pleura (Figure 4). The electrocardiogram, toward the end, was consistent with right ventricular strain. The patient died on December 2, 1957, after three weeks of repeated and profuse hemoptyses.

At autopsy, large dense adhesions were found in the left pleural space, and were most prominent at the apex. The left lung weighed 800 gm. Its pleura was dull

and rough, and measured 1.9 cm. over the apex. Both lobes of the lung showed congestion, edema, and areas of induration of a fibrous character. Tiny yellowish nodules were scattered throughout. The left upper lobe contained a 4 by 6 cm. cavity with partly necrotic walls; it was incompletely filled with necrotic tissue of a brownish color. The lower lobe showed several large emphysematous bullae. A moderate number of adhesions was present in the right pleural cavity. The right lung weighed 625 gm. and appeared to be markedly emphysematous. Several large cavities were encountered in the right upper lobe, the largest of which measured 4 by 3 cm. Smaller cavities were present also in the middle lobe. The adrenals were slightly decreased in size, but otherwise appeared to be normal.

Microscopic examination of sections taken from the lungs showed marked congestion, edema, focal emphysema, and fibrosis. Multiple small nodular formations of epithelioid and giant cells arranged in a swirl pattern were present throughout the lungs. Some of these nodules showed peripheral infiltration with lymphocytes. Sections taken through a cavity wall revealed thick, fibrotic and somewhat necrotic borders, infiltrated mostly with chronic inflammatory cells. Squamous metaplasia of the respiratory epithelium was noted in some areas. Acute inflammation adjacent to cavities and recent hemorrhage were noted in the right lung. Many of the cavity spaces were partly lined by squamous epithelium and appeared to be in direct communication with the bronchi. Within the cavities and within the small bronchioles were tangled filaments of fungus. In some areas these formed large granules. Cultures of these grew out *M. apiospermum.* Sections of hilar lymph nodes showed many nodular formations similar to the ones described in the lungs. Fibrosis involving large areas was noted. No evidence of caseation necrosis was seen. The spleen also showed many small nodules of epithelioid and giant cells, and the centers of many of these revealed fibrinoid degeneration. The final diagnoses were: sarcoidosis involving lungs, spleen, and lymph nodes; pulmonary fibrosis and emphysema; and secondary fungus infection, both lungs.

Mycologic Findings

The fungus grew well on all the media employed for primary isolation, including brain-heart infusion agar with blood, Littman's oxgall agar, and Sabouraud's dextrose agar. It grew readily in the presence of penicillin, 500 units/ml., streptomycin, 1,000 units/ml., or actidione, 0.5 mg./ml. The colonies were fast-growing, and produced a white, cottony aerial mycelium which later turned to a mouse-gray color. All isolations were those of the asexual form, *M. apiospermum,* showing ovoid and pyriform dark conidia produced singly at the ends of long conidiophores or from the sides of the mycelium on short conidiophores. Coremia, composed of bunches of conidiophores, also were found. The mycelia were broad and septate.

Attempts were made to induce perithecia production, typical of the sexual stage of *A. boydii.* After four months of incubation at room temperature, and the use of Sabouraud's dextrose agar, dark brown, thin-walled perithecia were recovered. When crushed and examined microscopically, the elliptical yellowish brown ascospores emerged from the ruptured perithecia. Three mice were given intraperitoneal inoculations of the fungus mixed with mucin. All three mice appeared to be in good condition for 25 days, at which time they were sacrificed. At autopsy, the appearance was grossly normal in all respects except that one mouse had developed a nodule, about 2 mm. in diameter, on its mesentery. A culture yielded the same fungus. Positive cultures were also obtained from the livers and spleens of all three mice. However, tissue sections made from these livers and spleens failed to disclose the fungus, and the only tissue changes were those due to post-mortem autolysis.

A sample of the fungus which had been passed through the above mice was then

used to inoculate five additional mice. Two died early, one on the seventh day and one on the thirteenth day. The livers, spleens, and kidneys of these mice contained multiple abscesses, up to 1 cm. in diameter. Direct examination of these abscesses revealed masses of mycelium but no granules. Tissue sections revealed areas of necrosis and abscess formation. In the spleen there were disruption of the cellular pattern and collections of chronic inflammatory cells and giant cells. The abscess in the kidney showed necrosis, cell debris, and infiltration with neutrophils, and scattered throughout the necrotic area were translucent, long, thin tubular structures resembling mycelial elements. The remaining three mice appeared to be in good physical condition, except for postural difficulties, until the twenty-first day, when they were sacrificed. All of the livers and spleens of these animals revealed many abscesses containing the fungus. Tissue sections of the brains of two of the mice were examined and appeared to be normal.

In vitro sensitivity tests of the fungus showed that it was susceptible to 0.005 mg./ml. of Win 4227,* to 2.6 μg./ml. of amphotericin B, and to 10 μg./ml. of hydroxystilbamidine. It was not inhibited by 50 μg./ml. of the following agents: penicillin, chlortetracycline, oxytetracycline, tetracycline, streptomycin, Chloromycetin, Magnamycin or Sigmamycin. Growth was inhibited by 50 μg./ml. of polymixin B, and by 125 μg./ml. of Mycostatin. Growth was not inhibited by 30 mg.% of nitrofurantoin, or by 1 mg./ml. of potassium iodide.

Discussion

A. boydii and *M. apiospermum* are different growth phases of the same fungus. Each phase was discovered separately, and as it was not realized for a number of years that they were the same organism, the two names became firmly established in the literature. When two supposedly different fungi are found to be merely the sexual and the asexual phases of the same fungus, the name of the sexual phase alone is usually retained.[2] Such has not been the case with *A. boydii,* probably because the vast majority of isolates of this organism have been in the asexual phase. The past history of *A. boydii-M. apiospermum* has been summarized by Ajello.[3] *M. apiospermum,* the asexual, imperfect, or conidial phase, was first isolated in 1909 by Tarozzi[4] from a case of mycetoma. The organism was given its name by Saccardo[5] in 1911. A number of other case reports followed, and the organism became familiar as a cause of mycetoma.

In 1921 Boyd and Crutchfield[6] reported the isolation of a new, perfect fungus from a case of maduromycosis of the foot, and this organism was named *A. boydii* by Shear[7] in 1922. Although it was suspected as early as 1934 that *A. boydii* and *M. apiospermum* were the same organism,[8] this was not proved until 1944, when Emmons[9] discovered that a subculture of a strain of *M. apiospermum* which he had in stock culture produced perithecia similar to those described for *A. boydii.* This observation was confirmed. However, since most isolates are in the asexual phase, it has been agreed that, for convenience, when the organism can be isolated in the sexual phase it is identified as *A. boydii,* but if cultured only in the asexual phase it is called *M. apiospermum.*[2] The asexual phase grows readily on standard culture media, whereas it is usually difficult to induce growth of the sexual phase.

A. boydii is one of the most clearly defined etiologic agents of mycetomas, and it is the most frequent cause of this condition in the United States.[10] There are reports also of this organism as a rare cause of otomycosis,[11] septicemia,[12] and

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meningitis,[13] and of the one other case of pulmonary infection.[14, 15] In addition, mention was made in a recent symposium on fungus diseases of a case of pulmonary mycetoma from which *A. boydii* was repeatedly cultured from the sputum,[16] but further details have not yet appeared.

Case reports of *A. boydii* infections usually describe some trauma which may have permitted the organism, along with a foreign body, to gain entry into the tissues. This suggests the probability that the fungus is a natural saprophyte, and this has been supported by numerous isolations of the organism from the soil,[3, 17] from a polluted stream, and from several sewage-treatment plants.[18] There are many pathogenic fungi which exist as saprophytes in nature,[19] *Histoplasma capsulatum* being one example. We do not know how *A. boydii* gained entrance to the lungs in our patient, but it seems probable that the organism was inhaled, and that it secondarily infected the previously formed cysts.

There is but one report of successful medical treatment of allescheriasis. Seeliger and Reifferscheid [20] reported an apparent cure of mycetoma due to the fungus after 11 months of oral and local treatment with 2',2-dioxy-5',5-dichlordiphenylsulfide. Surgical excision of the entire infected area has been considered to be necessary in other cases. The strain of *A. boydii* isolated from the other reported case of pulmonary infection initially showed in vitro sensitivity to Chloromycetin, and the patient improved briefly when this was given. In vitro resistance developed rapidly, however, and the patient became worse.[14, 15]

Mention has been made of factors [1] which probably predispose to the development of secondary fungal infections. The first of these is the presence of a debilitating illness which reduces the patient's resistance. As Longcope and Freiman have pointed out,[21] death in sarcoidosis is usually due to some complication, often a secondary infection. Reports of the association with sarcoidosis of blastomycosis,[22] coccidioidomycosis,[23] histoplasmosis,[25] cryptococcosis,[26] nocardiosis, moniliasis, and aspergillosis [27] indicate that fungal infections are not an unusual complication. The mechanisms which increase the susceptibility to infection in patients with sarcoidosis are not well understood. The only immunologic defect thus far demonstrated in sarcoidosis appears to concern the production or transport of antibodies involved in delayed-type skin reactions.[28] Hypogammaglobulinemia has been reported in one presumed case of sarcoidosis.[29] In our patient, the pulmonary insufficiency, the constant blood-letting in the form of persistent hemoptyses, and the repeated bronchopulmonary bacterial infections probably further handicapped his resistance.

The adverse effect that antibiotics may have on fungus infection [30] has been pointed out, and several possible mechanisms have been suggested. Superinfection through overgrowth of naturally occurring bacteria and fungi not suppressed by the antibiotic is apparently the principal one.[31, 32] The previously reported case of pulmonary allescheriasis received intermittent antibiotic therapy for several months before *A. boydii* was isolated.[14] Actual stimulation of growth of monilia has been demonstrated with chlortetracycline, bacitracin, and neomycin in vitro,[33, 34] but it is uncertain whether any such enhancement occurs in man. That antibiotics may alter the immunologic response was suggested when a depression of antibody titers was found in laboratory animals after prolonged feeding of antibiotics,[35, 36] but the survival time of these animals was not shortened, making the significance doubtful.[37] Direct tissue toxicity is suggested by a report

that a fungus infection is potentiated when both antibiotic and fungus use the same portal of entry.[38] Whatever the mechanism may be, our patient received courses of the various antibiotics for many months prior to the initial isolation of the fungus.

It is well recognized that the occurrence of infection is one of the hazards of prolonged administration of corticosteroids.[39] Plotz et al.[40] noted that infection was the leading cause of death in a large series of patients with Cushing's disease, and that use of antibiotic therapy did not appear to lessen this hazard. This danger seems to be heightened when prolonged corticosteroid therapy is used in a chronic debilitating illness commonly associated with an increased incidence of infection.[41]

The phenomenon of lowered resistance to infection from treatment with corticosteroids has been extensively studied, and numerous mechanisms have been proposed.[30, 39, 42] It has been shown experimentally that large doses of corticosteroids generally suppress inflammation and repair.[43] This diminution of inflammatory response occurs whether the stimulus be a chemical irritant or an immunologically active material.[39] The corticosteroids appear to act primarily on the blood vessel wall in such a way as to maintain vascular tone, reduce endothelial injury, and decrease capillary permeability. Endothelial adherence of leukocytes is minimized. Thus there is little outflow of cells and fluid into the injured area. Disturbance of the natural response to injury decreases the normal reparative function.[44, 45] The phagocytic function of leukocytes may also be decreased,[46] but this effect is probably not of great significance.[39] Corticosteroids have also been shown to depress antibody production,[47, 48] but since quite large doses are required to produce this effect, it is probably of little significance clinically.[49] Another mechanism proposed to explain the depression of resistance by corticosteroids is a disturbance of reticuloendothelial function.[48, 50]

It would thus appear that our patient had all the requisites for a secondary fungus infection. He had a severe, chronic, debilitating disease of the type frequently complicated by secondary infection, not unusually a mycosis. The repeated administration of various antibiotics and the prolonged corticosteroid therapy probably produced a profound ecologic disturbance, and were likely factors in the patient's inability to resist a usually saprophytic fungus. However, had our patient not received these drugs, he undoubtedly would have died much sooner of pulmonary insufficiency, cor pulmonale, or of an infection caused by a more mundane bacterial agent.

Summary

A case of pulmonary sarcoidosis complicated by an infection of the lungs with *Allescheria boydii* is presented. This complication occurred after repeated courses of antibiotics and prolonged corticosteroid therapy. The medical history of this fungus is reviewed, and the factors predisposing our patient to the development of this rare infection of the lungs are discussed. This is the second known case report of pulmonary allescheriasis.

Summario in Interlingua

Es reportate un caso mortal de infection pulmonar per *Allescheria boydii*. Le patiente esseva un fermero de racia blanc con sarcoidosis complicate per recurrente

infectiones respiratori, progressive insufficientia pulmonar e repetite hemoptyses. Su maladia habeva commenciate al etate de 30 annos, sequente un curso de approximativemente septe annos. Multe cursos de antibioticos esseva administrate durante un periodo de quatro annos. Therapia corticosteroidic esseva usate durante le ultime tres annos ante le morte. Le sputo esseva examinate periodicamente pro bacillos de tuberculose e pro fungos. Durante le ultime 10 menses del vita del patiente, il esseva constatate que le sputo contineva *A. boydii*. Le mesme fungo esseva culturate ab specimens necroptic de pulmon. Iste organismo es un causa commun de mycetoma. Illo ha etiam essite isolate in casos individual de otomycosis, septicemia, e meningitis. Secundo nostre informationes, le caso del presente reporto es solmente le secunde de *A. boydii* como causa de infection pulmonar.

A. boydii e *Monosporium apiospermum* designa le phases sexual e asexual del mesme fungo. Quando duo supponitemente differente fungos es recognoscite como mermente le phases sexual e asexual del mesme organismo, il es costumari retener solmente le nomine del phase sexual. Tamen, le vaste majoritate del isolatos de iste fungo ha essite effectuate in le phase asexual, e on se ha ponite de accordo que si le organismo pote esser isolate in le phase sexual illo es designate como *A. boydii,* sed si illo es isolabile solmente in le phase asexual, alora illo es designate como *M. apiospermum.*

In le presente caso, omne le isolatos del organismo esseva in le phase asexual, sed post plure essayos, un crescentia de illo in le forma de *A. boydii* esseva inducite. Iste fungo es un saprophyto natural. On lo ha isolate ab le terra, ab polluite aquas currente, e ab installationes pro le tractamento de aquas de cloaca. Nos non sape como *A. boydii* ganiava accesso al pulmones de nostre patiente, sed il es probabile que illo esseva inhalate e que illo inficeva secundarimente le preformate cystes.

Il pare que certe factores esseva presente in nostre patiente le quales predisponeva le a disveloppar iste infection. Ille habeva un debilitante morbo primari con extense alterationes in le pulmones, e un profunde perturbation ecologic esseva producite in consequentia de un perdurative tractamento con antibioticos e corticosteroides. On ha observate que simile factores es usualmente representate in casos de candidiasis, aspergillosis, e mucormycosis, e omne iste infectiones es generalmente incontrate in association con altere morbos primari.

Mortes in casos de sarcoidosis es usualmente causate per le un o le altere complication, e isto es frequentemente un infection secundari. Il non es un occurrentia inusual que iste infection es causate per un fungo. Es describite le effectos adverse que antibioticos pote haber in casos de infectiones fungal. Es proponite plure mechanismos possibile. Inter istos superinfection es apparentemente le plus significative. Le phenomeno del reducite resistentia contra infectiones post therapia corticosteroidic esseva studiate extensemente. Un numero de differente mechanismos possibile es proponite. Un suppression general del inflammation e del activitate reparatori, un diminution del functiones phagocytic in le leucocytos, un depression del production de anticorpore, e un perturbation del functionamento reticuloendothelial —omne istos ha essite observate in experimentos laboratorial, sed lor signification clinic non es ben comprendite.

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MEGALOBLASTIC ANEMIA DUE TO DILANTIN THERAPY*

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The occurrence of megaloblastic anemia following the use of anticonvulsant drugs has been reported in the British and Scandinavian literature. We believe the following case is among the first in the American literature.

Case Report

Since age 19, a 42-year-old white female had been admitted intermittently to state hospitals for treatment of a convulsive disorder, at times associated with psychotic manifestations. From December, 1951, to November 6, 1958, treatment had consisted of Dilantin, gr. 1½, three times a day, and phenobarbital, gr. ½, three times a day. This was reduced to twice a day from November 6, 1958, until December 4, 1958. From January 23, 1956, to January 18, 1958, the patient also received chlorpromazine, the maximal dose being 100 mg. three times a day; and from January 18, 1958, to December 4, 1958, trifluprομazine, the maximal dose being 25 mg. three times a day.

The patient was first seen, relative to the present report, on December 4, 1958, during a visit at Longview State Hospital for observation of the effect of antipsychotic and anticonvulsive medications. She was found to be extremely pale and weak, and was immediately re-admitted for study and treatment.

Physical examination on this admission showed only extreme pallor. The tongue showed no abnormality, and no significant neurologic findings were noted. Intensive questioning revealed no dietary abnormalities or lack of eating. The patient's daily diet contained meat (liver twice a week), other protein foods, and fresh fruit and vegetables, according to her own statement and the report of both the husband and the family.

Course in Hospital: At time of admission the red blood cell count was 1,660,000; hemoglobin, 4.5 gm.%; white blood cell count, 5,550; the differential revealed 78% neutrophils, 21% lymphocytes, and 1% monocytes. Because of the patient's extreme weakness and apathy, two units of blood were given. Repeat blood studies 24 hours later were as follows: red blood cells, 2,150,000; hemoglobin, 6.0 gm.%; hematocrit, 24%; reticulocytes, 3.3%; white blood cells, 6,450; differential: neutrophils, 85%; lymphocytes, 14%; monocytes, 1%; MCV, 111; MCHC, 25; MCH, 28. A sternal bone marrow examination revealed a megaloblastic and hyperplastic bone marrow. There was a relative diminution in the myeloid series in proportion to the erythroid series, and abnormally large metamyelocytes were fairly numerous (Figure 1). The platelet count was 182,000; bleeding time, 2½ minutes; clotting time, 4 minutes. The serum B_{12} level was low normal at 110 micro-micrograms/100 ml. Both the Diagnex test and the gastric intubation with histamine administration failed to reveal the presence of free acid in the gastric secretions. The blood urea nitrogen was 10 mg.%; serum creatinine, 0.7 mg.%. On December 5, 1958, the Schilling test (radioactive vitamin B_{12} absorption) was within normal range, showing 10% excretion in 24 hours. X-ray studies of the chest and the entire gastrointestinal tract were within normal limits.

* Received for publication August 28, 1959.
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After the initial emergency transfusions and the later diagnostic administration of 1,000 μg. of vitamin B_{12} during the Schilling test, there was gradual improvement. Fourteen days later the red count was 3,760,000; hemoglobin, 10.5 gm.%; hematocrit, 36%; white blood count, 9,600; differential: 77% neutrophils, with 19% lymphocytes and 4% monocytes. Clinically, the patient appeared to be stronger, and her color was markedly improved. The reticulocyte count rose to 16% on the eleventh day. Twenty-six days after the first bone marrow examination, a second determination revealed normal bone marrow. A repeat Schilling test was 16.8%. A white cell folic acid determination * was 0.039 micro-microgram (low normal)/10^6 white cells. The urinary folic acid determination expressed as glutamic acid was 145.9 mg. in 24 hours in unheated urine. This reduced to 31.6 mg. in 24 hours in the heated

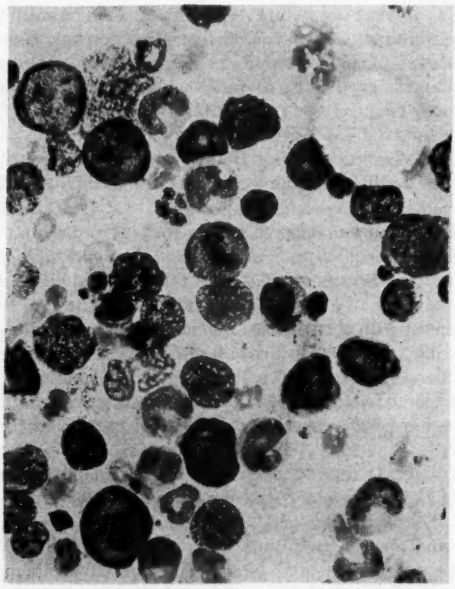

FIG. 1. Sternal marrow showing megaloblastic and hyperplastic bone marrow.

specimen. The results were interpreted to be within normal limits. Six weeks after admission, the red blood count was 4,750,000; hemoglobin, 12.4 gm.%; hematocrit, 36%. The serum iron was 38 μg.%. Oral iron was started at this time.

The patient improved rapidly during her hospital stay, having only two mild seizures. Dilantin sodium, gr. 1½, three times a day, was maintained; no other medication was given.

Megaloblastic anemia due to anticonvulsant drugs was first reported in 1954 by Badenoch,[1] who treated two epileptics with Dilantin (phenytoin, Epanutin) and phenobarbital. Hawkins and Meynell [2] reported another case in the same year, this patient being treated only with Dilantin. Another case of megaloblastic anemia was reported later that year by Chalmers and Boheimer,[3] but this patient had been taking Dilantin, phenobarbital, and also primidone (Mysoline). More

* Folic acid and B_{12} determinations were performed by Dr. John Will at the Hematology Laboratory of the Cincinnati General Hospital.

than 20 cases have since been reported where Dilantin was given along with other antiepileptic drugs. Primidone was the sole drug given to the two megaloblastic anemia patients by Fuld in 1955,[4] the two patients of Newman and Summer,[5] and the patient of Chanarin et al.[6] Mebaral (mephobarbital) was the

TABLE 1

Summary of Laboratory Data, Treatment and Progressive Improvement of the Patient

Date	RBC	HCT	Hb.	Retic.	WBC	Differential				Special Tests	Treatment
						P	L	M	E		
12/4/58	1,660,000	22	4.5		5,550	78	21	1			Transfusion 100 ml. bld.
12/5/58	2,150,000	24	6	3.3%	6,450	85	14	1		Bone marrow megaloblastic anemia	Dilantin 1½ gr. t.i.d.
12/8/58	2,660,000	25	6.5	4.7%	5,100	53	41	6		Serum B_{12} 110γγ/100 ml.	
12/9/58				2.7%						Platelet count, 182,000 Bleeding, 2'22" Clotting, 4'3"	
12/11/58				4.1%							
12/12/58										Schilling test (1,000 mg. B_{12}): 10% B_{12} excretion.	
12/13/58				15.9%							
12/14/58				15.6%							
12/15/58	2,560,000	28	8	16.1%	3,300	66	33	1			
12/17/58				9.2%							
12/19/58	3,200,000	35	9.8		5,100						
12/22/58				5.3%							
12/24/58				4.1%							
12/26/58	3,760,000	36	10.5		9,600	77	19	4			
12/29/58				2.3%							
12/30/58				3%						Gastric analysis: no free acid	
1/2/59	3,560,000		12	1.8%	8,050					Repeat bone marrow: normal	
1/6/59	3,460,000		12		8,750					Schilling test: 16% excretion	
1/7/59										WBC folic acid 0.039 $9/10^6$. Urinary folic acid, 145.9 mg. 24 hrs. glutamic acid. Reduced to 31.6 mg. in 24 hrs. in heated specimen	
1/12/59	3,530,000	35	11		7,350	68	27	4	1		
1/15/19	3,660,000	35	12		5,500						
1/20/59	4,070,000	37	12		5,350	63	32	5			
1/23/59	4,750,000	36	12.4		9,200					Serum iron, 38 μg.%	

sole antiepileptic drug given in the case reported by Calvert et al.[7] Phenobarbital has not been reported as the sole etiologic agent of megaloblastic anemia in epileptics. At Longview State Hospital, more than 5,000 patients have been treated with phenothiazine derivatives in the last five years, with no other in-

stances of megaloblastic anemia having occurred. These data probably exonerate chlorpromazine and trifluprom azine as etiologic agents in this case.

To our knowledge, only one case of megaloblastic anemia has been reported to have occurred in this country. This patient, described by Christenson et al. in 1957,[8] was on primidone.

It is accepted thought that pernicious anemia does occur in epileptics and must be ruled out by: (1) studies of cobalt 60 B_{12} absorption; (2) absence of free gastric hydrochloric acid; (3) serum B_{12} levels; (4) gastric mucosal biopsies, and (5) therapeutic response to B_{12} or folic acid. Free hydrochloric acid was present in most of the cases reported to date,[1-7, 9, 10, 12, 14-16] but was absent in one case,[1] and aspiration was not performed in the remainder. Gastric mucosal biopsies were normal in three cases.[1, 8] Cobalt 60 B_{12} absorption studies were normal in six cases.[1, 6, 7, 9, 13] Serum B_{12} levels were quite low in two cases,[14] low-normal in three cases,[1, 6, 7, 10] and normal in four cases.[1, 6, 9, 16] Response to B_{12} therapy alone was noted in eight patients,[1, 5, 7, 9, 14-16] as well as in our own case. Response to folic acid alone occurred in 16 cases.[1, 2, 4-7, 9, 11-16] In eight of the 16 cases, B_{12} had been previously but unsuccessfully administered. One interesting case of Hawkins and Meynell [8] did not respond to either B_{12} or folic acid, and possibly represents a different type of refractory anemia. The role of transfusion in most of these cases, as well as in our own, has not been evaluated.

TABLE 2

Medications Received

Date	Dilantin	Phenobarbital	Trifluprom azine
Jan. '51–11/6/58	gr. 1½ t.i.d.	gr. 1½ t.i.d.	
11/6–12/4/58	gr. 1½ b.i.d.	gr. ½ b.i.d.	
1/23/56–2/8/56		25 mg. t.i.d.	
2/8/56–2/13/56		50 mg. t.i.d.	
2/13/56–1/18/56		100 mg. t.i.d.	
1/18/58–3/13/58			20 mg. t.i.d.
3/13/58–12/4/58			25 mg. t.i.d.

A very interesting study on a large colony of epileptics was reported by Hawkins and Meynell in 1958.[9] The mean corpuscular volume (MCV) of a treated group of epileptics was 92.2, in contrast to 86.6 for one control group and 88.7 for another control group. Serum B_{12} levels were the same in the epileptics as in the control group. Weekly doses of 100 mg. B_{12} for three months did not affect the MCV of the epileptic group, but 20 mg. folic acid daily for one month reduced the MCV to normal. Subacute combined degeneration did occur in two of the megaloblastic anemia cases reported by Hawkins and Meynell.[9]

Dietary deficiencies of folic acid or B_{12}, and also the malabsorption syndrome, such as occurs in sprue, have to be ruled out in these patients. Cobalt 60 B_{12} absorption studies, as well as trioleic acid I^{131} absorption, should rule out the malabsorption group. Dietary adequacy, however, is difficult to prove.

The etiology of the megaloblastic anemia induced by antiepileptic drugs seems to be a derangement of folic acid or B_{12} metabolism, somewhat similar to that induced by amethopterin and other folic acid antagonists. The derangement is

easily overcome by administering an excess of B_{12} or folic acid without stopping the offending drugs. Studies of folic acid absorption and excretion have shown no definite abnormalities. This has also been true of B_{12} level and absorption studies.

Conclusion

The present case and those in the literature point to the importance of periodic blood counts in patients receiving anticonvulsant drugs. Whether prophylactic folic acid should be administered to all such patients is a moot point. There is always the danger that pernicious anemia as a cause of neurologic complications would be masked by such use of folic acid.

Summary

A case is reported of megaloblastic anemia due to Dilantin therapy, with subsequent response to vitamin B_{12} therapy. The literature has been reviewed, and attention has again been called to the fact that megaloblastic anemia is a rare complication of anticonvulsant therapy. The anemia does not relapse if the original drugs are continued with the addition of vitamin B_{12} or folic acid.

Summario in Interlingua

Un femina de racia blanc de 42 annos de etate qui habeva epilepsia esseva tractate con Dilantina durante sex annos e disveloppava anemia megaloblastic. Determinationes de acido folic in sanguine e urina, del nivellos seral de vitamina B_{12}, e le test de Schilling esseva omnes intra le limites del norma. Le historia dietari revelava nulle inadequatias. Un responsa progressive e le melioration del numerationes sanguinee usque a nivellos normal sequeva le administration de vitamina B_{12} durante le test de Schilling. Es opinate que iste caso es inter le primes de anemia megaloblastic post le uso de Dilantina in le litteratura american. Altere casos causate per drogas anticonvulsional se trova in publicationes britannic e scandinave. Le etiologia es discutite. Il pare tractar se de un disrangiamento del metabolismo de acido folic o de vitamina B_{12}. Le condition es facilemente corrigite per le administration de un excesso de vitamina B_{12} o de acido folic durante que le administration del incriminate droga non es interrumpite. Es signalate de novo que anemia megaloblastic es un complication rar de therapias anticonvulsional e que il occurre nulle recidiva del anemia si le drogas original es continuate con le addition de vitamina B_{12} o acido folic.

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EDITORIALS

TOWARD AN EDITORIAL NEW STEADY STATE

THE editing of a journal (such as the ANNALS) lends itself to analogy with certain biologic processes. A healthy journal like a healthy organism is in a state of dynamic equilibrium. Output of energy must equal input of energy; randomness of effort must be diminished (less entropy), useful work must be done. The functional goal of the ANNALS organism, the useful work, has been presented already in an earlier editorial. Let us state it again: it is to help the physician to become a better physician by efficiently conveying to him stimulating ideas and useful knowledge.

In terms of metabolic balance, output must equal intake; the sum of manuscripts accepted and rejected must equal those received, if a dynamic equilibrium is to be maintained. Excessive intake and retention of unprocessed papers quickly leads to editorial indigestion; excessive intake and retention of accepted papers to obesity of the "backlog." In analogy to renal clearance, the rate of publication (or the rate of excretion, UV) may be normal; but if the backlog (or concentration in plasma, P) is high, the clearance (UV/P) is low. A low editorial clearance associated with a high backlog of accepted manuscripts is unhealthy. In such a condition the journal is uremic, the contributors are frustrated, the readers are supplied with information slightly frosted o'er.

During the change-over of editorship the dynamic equilibrium of a journal inevitably is disturbed. As in a patient with a newly-transplanted kidney there is a temporary lag in excretory function with a resultant retention of metabolites; the new editors have had to treat retention of unprocessed manuscripts and obesity of backlog by increasing the rate of output. This therapeutic measure is being accomplished in several ways—by issuing a supplementary number and by increasing the rate of rejection, as well as the rate of publication, of manuscripts. We hope that contributors who have felt the sting of our editorial stringency will make some allowance for the necessities of this transient phase.

With this issue the half-life is passed of our inherited backlog of main articles; it will be at least three more issues before the same point is reached with respect to case reports. The Editor's objective is to attain a new steady state in which the average total period between receipt of manuscripts and their publication is six months or less—a steady state with normal clearance and healthy turnover.

Meanwhile, contributors, send us your papers on clinical studies or basic research, your case reports or reviews, and your ideas in any form. But expect the editors to be selective, for quality of nutrients, as well as quantity,

is of paramount importance to the normal metabolism of amoeba, man, or journal. Let us hear from you.

J. R. E.

ANNOTATIONS ON THE THIRTEENTH RHEUMATISM REVIEW

TWENTY-FIVE years ago the first systematic review of reports published in English on the various phases of the rheumatic diseases appeared in the ANNALS OF INTERNAL MEDICINE. The purpose, as stated by Dr. Philip S. Hench, the first editor, was "to prepare a correlated synopsis of the recent significant literature—including such editorial comments as may seem helpful." At intervals since that time a comprehensive analysis of clinical contributions and experimental investigations, with critical annotations prepared by an editorial committee of the American Rheumatism Association, has been published in this journal.

There is general agreement that the *Rheumatism Reviews* have served well to disseminate authoritative and current information in this rapidly expanding field of medical knowledge. For the practitioner and research worker they are a ready source of concise information on a great variety of subjects, including a comprehensive bibliography. They are a superb reference source. However, a rapid change has taken place. The original *Rheumatism Reviews,* which covered the American and English literature for 1932 and 1933, contained references to 465 reports. The current and *Thirteenth Review,* just published as Number 7 of Volume 53 of the ANNALS OF INTERNAL MEDICINE, makes reference to 3,430 published articles on arthritis, rheumatism, and allied diseases of connective tissues.

As the newer technics and methods of the basic sciences (bacteriology and immunology, biological and physical chemistry, electronmicroscopy, genetics, etc.) are applied to the many disorders of connective tissues it becomes increasingly more difficult to select the articles for review. The problem of keeping abreast of developments and trends in this subspecialty of internal medicine is increasing and can be expected to grow at an even faster rate. I would like to highlight some of the major developments in both the research and the clinical areas which are summarized in the current *Review.*

GENERAL

The terms "rheumatism" and "rheumatic diseases" are now accepted as synonymous and are used to indicate any painful disorder in which the primary symptoms are related to the articulations or the tissues surrounding them. The term "collagen disease" was originally designed to include systemic lupus erythematosus (S.L.E.), scleroderma, rheumatic fever, rheumatoid arthritis (R.A.), polyarteritis nodosa (P.N.A.), and dermatomyositis but its use has resulted in an indiscriminate acceptance of a term with diagnostic and pathogenic connotations not originally intended. It has

become a catch-all term for maladies with puzzling clinical and anatomic features. Since collagen is but one constituent of connective tissue and the other major components (ground substance and cells) may play an even more important role in the pathogenesis of these disorders, the more inclusive term "connective tissue diseases" is preferred by many writers.

More and better epidemiologic information is needed concerning the prevalence and incidence of rheumatic diseases. The actual prevalence of all types of arthritis is greater than was previously estimated. In Pittsburgh the prevalence of "classical arthritis" was 71 per 1,000 persons over the age of 14; that for "classical" plus "definite arthritis" was 218 per 1,000. A study of a population sample aged 55 to 64 years in Leigh, England revealed the following prevalence rates: all types of "chronic polyarthritis," 34.2%; "generalized osteoarthritis," 23.7%; R.A., 7.1%; mixed R.A. and osteoarthritis, 4%; ankylosing spondylitis, 1%; gout, 1%; and psoriatic arthropathy, 0.6%. To be reliable, prevalence estimates from different geographic areas will require greater precision and uniformity of diagnostic criteria. Progress in this direction has been the establishment of diagnostic criteria for rheumatoid arthritis by a committee of the American Rheumatism Association.

Rheumatoid Arthritis (R.A.)

It is possible to mention only a few of the numerous important contributions to our knowledge, understanding, and better control of this crippling disease. Significant advances recently made in four areas (prevalence, pathology, serologic reactions, and treatment) are worthy of special comment.

Prevalence: An analysis of the complete population of two health districts in South Wales based upon a positive history confirmed by laboratory or x-ray findings indicated that this disease is much more common than was realized heretofore. In the industrial area, R. A. was present in 4.9% of either males or females, and in the rural areas in 10.7% of females and 8.8% of males.

Pathology: The earliest anatomic change in the synovial membrane of R.A. is focal ischemia, due in part to an acute venulitis and capillaritis with fibrin thrombosis. Similar vascular changes have been demonstrated in subcutaneous rheumatoid nodules of seven days' clinical duration or less. The lesions of R.A. may involve most if not all parts of the body, but typically they involve synovial tissue, serous membranes, the uveal tract of the eye, and the skin. Focal connective tissue degeneration and necrosis associated with nodule formation in the myocardium, endocardium, sclerae, joint capsules, and tendon sheaths characterize this disease. Secondary amyloidosis has been reported in approximately 20% of autopsies in patients hospitalized for R.A.

Serologic Reactions: The demonstration by serologic reactions of an

abnormal gamma globulin in the serum of most patients with R.A. is a major development in this disease. This factor agglutinates, in higher than normal titers, a variety of substances (hemolytic streptococci, sheep and alligator erythrocytes, bentonite and latex particles) when the latter are treated first with certain protein fractions of normal human or sensitized rabbit serum. Numerous attempts currently are being made to improve the sensitivity of this reaction and to apply it as a diagnostic test. Using the most refined technics, 98% of patients with R.A. will give a positive reaction; however, no single test that is readily performed and practical gives results greater than 80 to 85% positive. The expectation of a test wholly specific for R.A. has not been realized and unfortunately the present tests are frequently positive in other collagen diseases, especially in S.L.E. The tests may not be positive, however, during the first several weeks or months of R.A., when the differential diagnosis is most difficult to make. They are usually negative in patients with rheumatoid spondylitis, juvenile R.A., rheumatic fever, gouty arthritis, and degenerative joint disease.

The abnormal protein responsible for this reaction has been designated the "rheumatoid factor." It has been isolated and physically characterized by ultracentrifugation as having a 22S sedimentation constant which can be dissociated into two fractions, one 19S, the other 7S. Using fluorescent technics, Mellors et al. have demonstrated that the rheumatoid factor is present in the plasma cells of the lymph nodes and in the lymphoid collections of the diseased synovial membranes of R.A. patients. Whether this intriguing reaction represents an antigen-antibody response remains to be determined. It is hoped that the current intensive investigations along these lines will shed new light upon the etiology or pathogenesis of R.A.

Some workers claimed never to have encountered a positive L.E. preparation in this disease, but the majority reported the occurrence of the L.E. phenomenon in 2% to 19% of R.A. patients. For practical purposes, a clinical diagnosis of R.A. should not be invalidated by a positive L.E. test; but a strongly positive L.E. test furnishes presumptive evidence against R.A. in a clinically undifferentiated problem.

Treatment: The consensus is that therapy for R.A. is best directed to the general management of all aspects of the patient's life, including his physical and emotional activity, by the use of pharmacologic, analgesic and anti-phlogistic agents, and physical therapy. Careful orientation of the patient by the physician concerning the nature of his disease is absolutely necessary for adequate management.

There are no therapeutic agents presently available that have been proved to prevent the ultimate destruction of joints (if this is to occur). Therefore, the choice of the analgesic and anti-inflammatory agents to be used depends upon the activity of the disease. If the symptoms can be controlled by drugs with minimal toxicity, there is no need to administer more potent and more toxic medications.

The variable natural history of R.A., with its spontaneous remissions and exacerbations and prominent psychological factors, make evaluation of individual therapeutic modalities difficult. Many workers are engaged in developing better methods to evaluate critically the therapeutic results of new agents. Of the drugs presently available salicylates, phenylbutazone, antimalarial compounds (chloroquine and hydroxychloroquine), gold salts, and adrenocortical steroids are effective. It is unfortunate that as yet we do not know how any of these drugs produce their therapeutic effect.

Salicylates remain the most useful drugs in the treatment of R.A. Phenylbutazone has proved to be of limited benefit as an antirheumatic agent. Although toxic reactions are comparatively rare, when compared to the total number of cases treated, they nevertheless must be borne in mind. The antimalarial compounds appear to suppress rheumatic activity in some patients, although the beneficial effects are slow to develop, usually being noted only after three to six weeks of therapy. Soluble gold compounds have been found useful in the treatment of many patients with R.A. and continue to be used by experienced and critical observers.

Although corticosteroids do not basically alter the fundamental pathologic process in R. A., their judicious use makes them valuable agents in the management of patients whose illness is resistant to other modes of therapy. The search for more effective and less toxic adrenocortical steroids continues. There is no convincing evidence that the newer steroids (triamcinolone, methylprednisolone, and dexamethasone) have any advantages over prednisone or prednisolone.

In the reports on corticosteroid therapy there was as much attention given to the complications of hormone administration as was given to the newer steroid drugs, their mode of action, methods of administration, therapeutic results, and the comparative effect of steroids, corticotrophin, and combined steroid and corticotrophin therapy. A simple listing of the most frequently reported untoward side-effects of corticosteroid therapy—mental disturbances, diabetes mellitus, purpura, hypertension, edema, vasculitis and neuropathy, osteoporosis, infection, peptic ulcerations with or without hemorrhage and/or perforation, and induced adrenal cortical insufficiency—will point up the problem. The frequency and severity of complications are correlated well with the dosage and duration of therapy. There is a strong tendency to reserve steroid therapy for those patients in whom the rheumatoid process shows continuing activity despite an adequate trial of salicylates and other antirheumatic drugs. The dose is then limited to that level which will permit the patient some relief of pain and no attempt is made to completely suppress the disease.

Rheumatoid Spondylitis

The age-old question of whether rheumatoid spondylitis is a separate entity or a variant of R.A. is still not settled. The striking differences in

sex incidence, the absence of serologic evidence of rheumatoid macroglobulins in the spondylitic patient, and above all the obvious differences in clinical features, natural course, and complications point strongly to a separate and distinct etiology and pathogenesis. The editors of the *Review* strongly recommend that these diseases should be distinguished clearly and that, to avoid unnecessary confusion in future published reports, they be listed as separate clinical entities.

The high incidence of aortic valve damage in rheumatoid spondylitis appears to be established. This lesion is distinct from rheumatic aortic valve disease because there is little tendency for the valve cusps to fuse. Fibrosis of the myocardial septum, fusion and thickening of the chordae tendineae, and fibrosis of the left auricular endocardium were rarely found. The intimal plaques found in spondylitis are never seen in rheumatic valvulitis.

Another interesting problem has arisen with the description of the increased frequency of leukemia from radiation therapy of patients with rheumatoid spondylitis. Large series of patients from three centers in Great Britain, Canada, and the United States clearly indicate that x-radiation plays a definite role in producing leukemia. Since the chief effect of this agent is analgesia, it would seem unwise at the present time to risk the development of leukemia by its continued use unless all other forms of symptomatic treatment have failed.

Gout

Important advances in recent years have increased knowledge of the basic defect in gout and have improved therapeutic programs. Today it is not sufficient to say that a patient has gout. It is now apparent that defects in uric acid metabolism leading to acute gouty arthritis, bursitis, or tendinitis may (1) be due to a hereditary factor of uric acid overproduction (primary gout), or (2) be associated with a markedly accelerated production and breakdown of blood cells (secondary gout).

The cause of hyperuricemia in primary gout is still unknown. For years it has been assumed that most of the uric acid resulted from the degradation of foods rich in purines and nulcleoproteins. Studies using isotope-labeled N^{15} have shown unequivocally that uric acid is also synthesized from simpler substances such as glycine, aspartic acid, glutamine, carbon dioxide, and "formyl" groups. Further studies using labeled glycine have shown that gouty subjects have an increased incorporation of glycine into uric acid and that these patients often excrete twice as much uric acid as do normal subjects. These studies suggest that a "shunt" mechanism is responsible for the overproduction of uric acid in gouty subjects. Since concurrent studies of renal clearance of uric acid in gouty subjects showed no differences from normals, this overproduction of uric acid is presumed to be the chief metabolic error.

Because not all patients with gout show overproduction of uric acid, the possibility of renal defects in gout has been reinvestigated. It has been shown that normal subjects have a higher clearance of uric acid when the serum urate level is raised to levels comparable to that of gouty patients. It has also been suggested that the most likely explanation for hyperuricemia is that precursors of uric acid are not used for other metabolic pathways in the gouty patient and hence more building blocks are available for the synthesis of uric acid. Observations in patients with secondary gout support this hypothesis.

With regard to treatment, colchicine remains the preferred drug for relief of the acute attacks of gout. Less than 5% of severe attacks fail to respond to the first full course of colchicine or require either a second course or some other agent. Attacks can be rapidly terminated by the administration of colchicine intravenously. Fewer gastrointestinal toxic effects accompany the use of colchicine intravenously, but the absence of these warning symptoms could increase the hazard of accidental overdose. Phenylbutazone is an effective drug in acute gout and is the drug of choice of many investigators. It is especially useful for patients intolerant to or unresponsive to colchicine.

In recent years it has been clearly established that by protracted treatment with suitable uricosuric drugs the formation of new tophi can be prevented, existing tophi can be made to shrink in size or to disappear, and the frequency of acute attacks of gouty arthritis can be reduced or prevented entirely. Such ideal results constitute a major therapeutic advance in this ancient disease. The list of effective oral uricosuric drugs of proved value in chronic gout has increased rapidly in recent years. It includes probenecid (Benemid), sulfinpyrazone (Anturan), and zoxazolamine (Flexin). All of these drugs have in common the property of increasing the urinary excretion of urates by blocking the renal tubular reabsorption of uric acid. Few patients fail to respond to adequate doses of probenecid. The causes for such failures include intolerance because of urticaria or gastric distress, and failure to achieve normal levels of serum urate because of severe impairment of renal function. Two new drugs of high uricosuric potency are now available. Sulfinpyrazone is an analog of phenylbutazone and is approximately six times as potent as probenecid on a weight basis. Zoxazolamine was first introduced as a skeletal muscle relaxant but has been shown to have marked uricosuric properties. There is some evidence that there may be some advantage from combining these latter drugs to accomplish the maximal urate diuretic effect.

Chlorothiazide (Diuril) has definite hyperuricemic properties. There have been reports of acute gouty arthritis precipitated by chlorothiazide and in several instances the patients had a past history suggestive of gout. Such attacks of gout have responded promptly to colchicine therapy. The action of chlorothiazide is probably due to the fact that it shares a common urinary

transport mechanism with uric acid and appears to block competitively the renal tubular secretion of uric acid.

Systemic Lupus Erythematosus (S.L.E.)

In the first *Rheumatism Review,* S.L.E. was considered a rare disease and was disposed of merely by listing it along with certain skin diseases as an occasional cause of joint symptoms. Ten years later (*Ninth Rheumatism Review,* 1941–1945) there was a marked change of attitude and "unusual interest in this disease was reflected by the publication of 52 reports with many general discussions." The relative frequency of and interest in S.L.E. continues to increase at a phenomenal rate and in the current *Review* discussion of this entity covers five pages. There was great concern expressed over the apparent rising incidence of the disease. This apparent change is due, in part, to a difference in the criteria used for the diagnosis of S.L.E. and particularly to the widespread application of the test for the L.E. phenomenon. Since more benign cases of S.L.E. are now being diagnosed as a result of the L.E. cell test and a higher index of clinical suspicion, many established concepts concerning this illness must be changed.

Controversy exists as to the specificity of the L.E. cell test. Very competent students of this disease have searched for L.E. cells in numerous diseases other than S.L.E. and have failed to find unequivocally positive reactions. Other equally able investigators have found L.E. cells in patients with penicillin and tetanus serum sensitivities, the hydralazine syndrome, phenylbutazone sensitivity, post-necrotic cirrhosis and tuberculosis. Other experienced clinicians report positive L. E. cell tests in from 3 to 15% of patients having untreated R.A. and in a greater percentage of those treated with adrenocortical steroids. The consensus is that positive L.E. cell tests occur in a wide variety of diseases other than S.L.E.

It has long been recognized that the serum of patients with S.L.E. frequently gives a positive serologic test for syphilis but has a negative treponema immobilization test. Many patients with a known false-positive serologic test for syphilis have been shown to develop subsequently either S.L.E., rheumatoid arthritis, or another "connective tissue disease." It appears to be established that changes in the serum protein may precede by many years the development of clinical signs of S.L.E. or a positive L.E. cell test. Recent systematic studies of close relatives of patients with overt S.L.E. have revealed a high incidence of clinically evident major rheumatic disease. In this investigation approximately one-quarter of the parents and siblings showed hypergammaglobulinemia; lesser numbers exhibited positive latex fixation reactions and biologic false positive reactions in tests with cardiolysin, and one had a positive L.E. cell reaction.

Miscellaneous and Experimental Arthropathies

An understanding of the pathologic physiology of even an obscure form of arthritis may provide insight into the pathogenesis of the more common

forms. Ochronotic arthritis results from a hereditary disturbance, characterized by the excretion of large quantities of homogentisic acid in the patient's urine. Recently it has been demonstrated in alcaptonuria that there is a metabolic block due to the lack of the enzyme, homogentisic acid oxidase, in the patient's liver. Alcaptonuria has thus been shown to be another example of an inherited disorder like galactosemia, phenylketonuria, and glycogen storage disease each of which is attributable to a defect in a single enzyme system. Family studies suggest that the defective gene may be dominant, with incomplete penetrance.

An entity which frequently goes undiagnosed is the carpal tunnel syndrome. It is caused by the compression of the median nerve beneath the volar carpal ligament with the production of acroparesthesias. A wide variety of lesions including R.A., tenosynovitis, gouty tophi. Leri's pleonosteosis, and the shoulder-hand syndrome with sclerodactyly may cause pressure on the nerves at the wrist and lead to this syndrome. Gratifying results follow simple surgical section of the volar carpal ligament.

A number of bizarre, apparently unrelated, and poorly understood disorders involving the musculoskeletal structures continue to be reported. The term "stiff-man syndrome" has been proposed for a disorder characterized by progressive, fluctuating muscular rigidity, with spasms at times approaching the severity of tetanus seizures, leading to rigid deformities of the neck, trunk, and limbs. Muscle biopsies have shown no abnormality, although a myopathy was suggested by one autopsy report. The electromyographic patterns are those of prolonged contraction of normal muscle. The 19 cases now reported suggest that the syndrome may be due to a metabolic disorder or possibly to a myopathy of undetermined nature.

Among the other odd entities included in this latest *Review* are nodular panniculitis, pigmented villonodular synovitis, osteitis pubis, tennis elbow, and a previously undescribed condition seen in children which has been given the appropriate designation "hoola-hoop syndrome."

Research in the rheumatic diseases has been hampered by the absence in animals of illnesses comparable to the human disease. Important advances have been made in an investigative approach to this problem and merit attention. A polyarthritis in rats which "simulates" R.A. has been produced by the injection of a Freund type adjuvant. The immunologic pathogenesis of this experimentally induced disease in rats is suggested by a regular latent period of 10 to 16 days between the injection of the microbacterial adjuvant and the onset of the arthritis, a shortened latent period following the reinoculation of adjuvant, and a flare-up following the injection of tuberculin in convalescent animals. This induced arthritis is probably a disseminated hypersensitivity reaction of the delayed type. Although simularities to the pathology of human R.A. are noted, the identification of such changes with any human counterpart is unwarranted.

The purpose of this brief résumé has been to direct attention to a few of the advances in this rapidly expanding field of diseases of the connective

tissues. The number of reports dealing with every phase of this subject, especially the highly technical ones, has grown rapidly and can be expected to increase at an even faster rate. Up until now the scope of the *Rheumatism Reviews* has been broad and comprehensive with the aim of including every worth-while paper contributing new knowledge, be it basic or clinical.

The practitioner is finding it increasingly more difficult, if not impossible, to select from this mass of factual reports such new information as would be helpful to him in the care of his patients. A solution to this problem would be the preparation of two types of reviews. The one would be intended for the practitioner of medicine who is interested in keeping abreast of new developments and trends in this field. The preparation of such a review for the use of clinicians would require that the editorial board recognize the significant contributions and stress their practical applications. The other review would be an all inclusive type planned to meet the needs of research workers in both the basic sciences and clinical aspects of the rheumatic diseases. This would be comprehensive and technical and serve as a reference source for anyone seeking detailed information relative to new methods and technics. The time has come to make a decision about the future of the *Rheumatism Reviews*.

CHARLEY J. SMYTH, M.D., F.A.C.P.

BOOK REVIEWS

Metal-Binding in Medicine: Proceedings of a Symposium Sponsored by Hahnemann Medical College and Hospital, Philadelphia. Editor: MARVIN J. SEVEN; Asciate Editor: L. AUDREY JOHNSON. 400 pages; 26 × 18.5 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $13.75.

Two main types of symposia are being published today—one type correlates ideas and data already known to the participating groups of specialists, and the other reports data which are original with regard to observation and interpretation. The book under review belongs largely to the latter category. Its general theme is dealt with in chapters ranging from the stoichiometry, stereochemistry, and thermodynamics of chelation to the role of metals and metal chelates in the disorders attributed to them. The chapter on distribution of trace metals in the human by Dr. Tipton is an impressive collection of analyses which both researcher and clinician will be pleased to find so conveniently assembled in one place. Among the new information presented, for example, are data on the stability of bismuth chelates in the body (the contribution of Drs. Johnson and Seven). There are many other such contributions. The editors have conscientiously provided many cross references and critical explanations.

This book is the only one known to this reviewer which contains a catalog of diseases ascribed to faulty metal-binding in the human body. For the clinical researcher who will encounter such disorders this treatise will serve both as a reference book and as a clinical review. To the clinical chemist it will be a guide to analytical methodology. The many tables, one of which illustrates the structures of most chelating compounds, will prove helpful to clinician and researcher alike. The book can serve as a source of information on base line values as well as a guide to the treatment of those disorders which are currently ascribed to faulty metal-binding in the human body.

MORITZ MICHAELIS, PH.D.

Care of Children in Hospitals. By the COMMITTEE ON HOSPITAL CARE OF THE AMERICAN ACADEMY OF PEDIATRICS. 96 pages; 23 × 15 cm. (paper-bound). 1960. Published by the American Academy of Pediatrics, 1801 Hinman Avenue, Evanston, Ill. Price, $1.50.

This little book is timely, because it discusses the trepidation that most physicians and hospital administrators feel when they deal with ill children who require hospitalization. The words, "We are not equipped . . ." and "We are not prepared . . ." are heard by pediatricians whenever they make admission arrangements with hospitals. Perhaps the greatest service this manual can perform is to reassure these institutions that they are well prepared and well equipped and can give good care to sick children.

The chapters deal in succession with such problems as the responsibility of the general hospital for child care, the functions of the pediatric service, planning for a pediatric unit, preparation of the child for surgery, the communicable diseases, the emotional needs of hospitalized children, the hospitalized adolescent, as well as laboratory services, child feeding, and the education and training of personnel. An appendix discusses patient identification, medico-legal considerations, forms and records, and the out-patient and emergency departments. Nuggets of forgotten or little-known information are provided, and there are blunt statements of the obvious. The latter are essential because the obvious is so often forgotten; for example, "Pediatrics is one of the four basic services. It should have representation on the

executive committee of the staff;" "Venipuncture in the young calls for special skill;" and "Every pediatric unit has a nurses' station. It should be placed to permit a view of all the patients' rooms."

This reviewer would like to see in the book a stern warning against excessive and aimless laboratory work, especially since more important details of examination are commonly neglected, such as the patient's height, blood pressure, and state of vision, hearing, and teeth. There should be additional emphasis on the need for visibility of all patients from the nurse's desk, particularly in view of the present trend in hospital design toward long, narrow groups of opaque-walled rooms equipped with unreliable electric signal devices, a trend which is dangerous for adults and very dangerous for children. [Designers might reconsider the safety and simplicity of the old square ward with its high ceiling and nurses' desk in the center.] Perhaps the book should plead also for simpler record keeping and less clerical responsibility for the nurse. Finally, in future editions, we hope that some oracle will be able to tell us how to use the stethoscope, the sphygmomanometer, and the fountain-pen at the bedside without spreading infection.

This book should help hesitant hospitals to improve their service to children and apathetic hospitals to raise their standards.

GRANGE S. COFFIN, M.D.

Cirrhosis of the Liver. By MARTIN S. KLECKNER, JR., M.D. 725 pages. 1960. Charles C Thomas, Springfield, Illinois. Price, $24.50.

This book, prepared for the clinician, is a comprehensive source of information about all types of cirrhosis. Historic background, experimental studies, pathology, clinical features, and treatment are covered. The author's wide personal experience and careful documentation from the literature give authority to the subject matter. The chapter on "Classification of Cirrhosis" should be especially helpful. The arrangement of material and the extensive references result in redundancy in some sections. The experimental and clinical effects of alcohol on the liver, as well as some recent therapeutic advances in management of ascites and hepatic coma, are mentioned only briefly.

The binding, the printing, and the illustrations are very satisfactory, although the index would be more useful if enlarged.

The internist with a special interest in the liver will want this volume on his shelf. For the busy practitioner, however, several other recently published works on liver disease present this material more concisely.

H. PHELPS POTTER, JR., M.D.

A Primer of Electrocardiography. 4th Ed. By GEORGE E. BURCH, M.D., F.A.C.P., and TRAVIS WINSOR, M.D., F.A.C.P. 293 pages; 24 × 16 cm. 1960. Lea & Febiger, Philadelphia. Price, $5.00.

Fifteen years have passed since the first edition of this work was published. As in prior editions, the authors have directed their book to beginners in electrocardiography. Controversial problems are omitted, and only well established concepts are included. It is clearly written, well presented, and should be of great value to all students being introduced to the subject.

The revisions made since the third edition of five years ago have not been extensive. A few new illustrations have been added and brief discussions have been included in the text. The changes represent no fundamental alterations. This work continues to be one of the most popular available for all beginners interested in electrocardiography.

LEONARD SCHERLIS, M.D.

Endemic Goitre. World Health Organization Monograph Series No. 44. 1960. Geneva, Switzerland. 481 pages printed in English. French and Spanish editions in preparation. 24 × 16 cm. Price, $8.00, cloth-bound. (Paper-bound edition also available.) Available in the U. S. through the Columbia University Press, International Documents Service, 2960 Broadway, New York 27, New York.

The problem of prophylaxis and treatment of endemic goiter has long been of world-wide significanee and, as such, it has been of special interest to the World Health Organization. The experiences of the past decade, particularly those concerned with education of the peoples of the world with regard to the measures necessary for the prevention of endemic goiter, are the basis for this publication.

The present monograph provides a comprehensive and complete review of the subject with contributions from 18 authors representing 10 different countries. Structurally, the monograph consists of 12 chapters, the first six of which were originally published as an interim report by the World Health Organization in 1958. These have been revised by their respective authors for this more recent and complete publication. The subject of endemic goiter is more than adequately covered by chapters devoted to the history, prevalence, and geographic distribution of the disease; its health significance, physiology, pathologic anatomy, and etiology; data on experimental studies; discussion of the iodization of salt and the principles and practice of endemic goiter control; and legislation on iodine prophylaxis. A complete subject index is appended, and the reference value of the book is further enhanced by the inclusion of pertinent references to the material presented at the end of each chapter.

The primary value of this type of publication to the average internist in the United States would appear to this reviewer to be in the role of a complete and recent reference volume dealing with the many aspects of the problem of endemic goiter.

JOSEPH B. WORKMAN, M.D.

BOOK NOTICES

Proceedings of The Eleventh Annual Conference on The Nephrotic Syndrome. Edited by JACK METCOFF, M.D. 324 pages; 28.1 × 23 cm. National Kidney Disease Foundation, New York. 1960.

This volume covers many topics not even implied by its title. Papers by Ullrich, Bodil, Schmidt-Nielsen, and Gottschalk give the theoretical and experimental bases, developed in the past decade, for the renal countercurrent mechanism for urine concentration. Studies pertinent to the renal reabsorption of sodium are presented by Wilde, Leaf, and LeBrie. The bulk of the volume, however, is occupied by a large group of papers on histologic, immunologic, and physiologic studies in a variety of experimental nephritides.

Of immediate interest to the clinician are short papers on inclusion-containing cells in the urinary sediment, the pathogenesis of pyelonephritis, postural proteinuria, and the treatment of the nephrotic syndrome.

The editors indicate, in the discussion of the papers, when the symposium audience laughed. The reader will be less moved by these jollities, unless he is of this coterie of kidney men, than by the canned guffaws of television's domestic dramas.

The publishers have wisely printed this volume by the photo-offset process from typescript and bound it with plastic rings, giving potential readers the benefits of lower cost and wider distribution, if not of the durability of incunabula.

E. J. H.

The Dispensatory of the United States of America. 1960 Edition. New Drug Developments Volume (Volume 2). ARTHUR OSOL, Ph.G., B.S., M.S., Ph.D., Editor-in-Chief, and ROBERTSON PRATT, A.B., Ph.D. 240 pages; 25.7 × 18.5 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $9.00.

Floods of new drugs pour onto the pharmacologic landscape year by year. Older streams remain, but their courses shift, diverted by rocks of newly-uncovered toxicities and silted by damp enthusiasms. The physician looks down on this scene with view dimmed by torrents of drug-house brochures. How is he to judge the lie of the land?

This suppiement to *The Dispensatory,* 25th Edition, may give him the perspective he needs. Two hundred nine articles give concise and objective descriptions of drugs released in the last five years and of older drugs for which new evaluations can be written. Each article gives the generic name of a drug, its chemical and trade names, the structural formula, a clear description of its physical and chemical properties, actions, uses, toxicities, and dosage data. Among the articles are extensive reviews of families of drugs, such as the hypoglycemic sulfonylureas and biguanides and the antibiotics.

This volume should be in every medical library and on the desk of every physician who wants therapeutic competence.

E. J. H.

Genetics: Genetic Information and the Control of Protein Structure and Function. Transactions of the First Conference, October 19, 20, 21 and 22, 1959, Princeton, New Jersey. Edited by H. ELDON SUTTON, Ph.D. 229 pages; 23.6 × 15.8 cm. The Josiah Macy, Jr. Foundation, New York. 1960. Price, $6.00.

The three colloquia of this conference deal with current research in the relation of chromosomal structure to its replication function, the genetic determination of protein structure, and agents modulating the biochemical expressions of genetic systems.

Two topics covered should be valuable to the hematologist. The structures of the abnormal hemoglobins are discussed in the second colloquium, and the third colloquium takes up the biochemistry of glucose-6-phosphate dehydrogenase deficiency in red cells in the drug-induced hemolytic anemias.

The reader who is not familiar with the methods and terms of biochemical genetics will find these discussions to be slow reading; the novice in this field will find simpler and more direct introductions to these problems elsewhere.

E. J. H.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. So far as is practicable, those of special interest will be selected for review later, but it is not possible to discuss them all.

Atlas of Hematology. By KATSUJI KATO, Ph.D., M.D. 290 pages. 1960. Grune & Stratton, New York. Price, $25.00.

Chemotherapy in Emotional Disorders. By FREDERIC F. FLACH, M.D., and PETER F. REGAN, III, M.D. 282 pages. 1960. McGraw-Hill Book Company, Inc., New York. Price, $10.00.

Congenital Malformations. (Ciba Foundation Symposium.) By G. E. W. WOLSTENHOLME, O.B.E., and CECILIA M. O'CONNOR, B.Sc. 292 pages. 1960. Little, Brown and Company, Boston, Mass. Price, $9.00.

Dictionary of Word Roots and Combining Forms. By DONALD J. BORROR. 134 pages; 12.8 × 17.8 cm. (paper bound). 1960. N-P Publications, Palo Alto, California. Price, $2.00.

Dietary Protein in Health and Disease. By JAMES B. ALLISON, Ph.D., and WILLIAM H. FITZPATRICK, Ph.D. 71 pages; 15.5 × 23.5 cm. 1960. Charles C Thomas, Springfield, Illinois. Price, $4.50.

Diverticulitis. By SARA M. JORDAN, M.D., and RUSSELL BOLES, JR., M.D. 82 pages. 1960. Grune & Stratton, New York. Price, $4.75.

Epidemiologic Methods. By BRIAN MACMAHON, M.D., Ph.D., D.P.H., THOMAS F. PUGH, M.D., M.P.H., and JOHANNES IPSEN, C. M., Dr. Med., M.P.H. 279 pages; 16 × 24 cm. 1960. Little, Brown and Company, Boston, Mass. Price, $7.50.

Fundamentals of Chest Roentgenology. By BENJAMIN FELSON, M.D. 269 pages. 1960. W. B. Saunders Company, Philadelphia, Pa.

Handbook of Medical Treatment. 7th Ed. By MILTON J. CHATTON, M.D., SHELDON MARGEN, M.A., M.D., and HENRY BRAINERD, M.D. 568 pages. 1960. Lange Medical Publications, Los Altos, California. Price, $3.50.

Man and His Body. By BENJAMIN F. MILLER, M.D., and RUTH GOODE. 361 pages. 1960. Simon and Schuster, New York. Price, $5.95.

The Management of Fractures and Soft Tissue Injuries. By THE COMMITTEE ON TRAUMA, AMERICAN COLLEGE OF SURGEONS. 372 pages; 14 × 21.5 cm. 1960. W. B. Saunders Company, Philadelphia, Pa.

Medical and Biological Research in Israel. Edited by MOSHE PRYWES, M.D., Hebrew University of Jerusalem, Hadassah Medical School. 537 pages; 16 × 23.4 cm. 1960. The Women's Zionist Organization of America. Obtainable through Grune & Stratton, New York. Price, $8.00.

The Metabolic Basis of Inherited Disease. By JOHN B. STANBURY, M.D., JAMES B. WYNGAARDEN, M.D., and DONALD S. FREDRICKSON, M.D. 1424 pages; 16 × 22.5 cm. 1960. McGraw-Hill Book Company, Inc. Price, $30.00.

Modern Occupation Medicine. Editors: A. J. FLEMING, M.D., and C. A. D'ALONZO, M.D. Associate Editor: J. A. ZAPP, Ph.D. 552 pages. 1960. Lea & Febiger, Philadelphia, Pa.

Pseudomonas Aeruginosa Infections. By CLAUDE E. FORKNER, JR., M.D. 73 pages; 14 × 23 cm. 1960. Grune & Stratton, New York. Price, $5.25.

Review of Medical Microbiology. 4th Ed. By ERNEST JAWETZ, M.D., JOSEPH MELNICK, M.D., and EDWARD A. ADELBERG, Ph.D. 376 pages. 1960. Published by Lange Medical Publications, Los Altos, California. Price, $5.00.

Toward the Diagnosis of Congenital Heart Disease. By W. CARLETON WHITESIDE, M.D. 85 pages; 15.5 × 23.5 cm. 1960. Charles C Thomas, Springfield, Illinois. Price, $4.50.

Tumors of the Odontogenic Apparatus and Jaws. By JOSEPH L. BERNIER, D.D.S. 106 pages; 20 × 26 cm. 1959. Published by Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, D. C. Price, $1.00.

Year Book of Medicine, 1960–61. By DOCTORS BEESON, MUSCHENHEIM, CASTLE, HARRISON, INGELFINGER, and BONDY. 708 pages. 1960. Year Book Publishers, Inc., Chicago, Illinois. Price, $8.00.

You Can Prevent Illness. By EDWARD R. PINCKNEY, M.D. 152 pages; 14 × 21 cm. 1960. J. B. Lippincott Company, Philadelphia, Pa. Price, $3.50.